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ORIGINAL ARTICLES

NOTE ON SOME RESPIRATORY STUDIES MADE ON LATE STAGES OF GAS POISONING*

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THE nature of the disability in late stages of gas poisoning is uncertain. The physical examination of the majority of men who complain of symptoms which they believe are due to gas fails to reveal any signs of impairment of their heart and lungs. For the greater part, such patients suffer from subjective symptoms similar to those of the so-called effort syndrome. Three typical cases have been studied from the cardiorespiratory standpoint in my laboratory. I had hoped to extend these studies, but find it impossible to do so, and believe it advisable to present the results at this time.

The first patient studied was a returned British soldier, who was gassed with chlorine very early in the war, and had had a very checkered military and hospital career. When he was first seen by us, some twelve months after he was gassed, physical examination failed to reveal any impairment of his heart and lungs, save some bronchitis. At this time it was a question whether or not he was entitled to a pension. Indeed it was suggested that he was feigning incapacity to escape military service. His chief complaint was inability to work without becoming breathless and faint.

His respiratory exchange, minute volume of air, depth and rate of respiration, tension of carbon dioxide in the alveolar air and that in equilibrium with his venous blood (affluent blood of the lungs), were determined at rest, walking, and running at a dog trot for a short distance; and compared with those of a normal man. At rest practically normal figures were obtained, but on ex-

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ercise his minute volume of air, in comparison with the degree of work done as measured by the oxygen consumption, was greater and out of all proportion to that obtained in the normal being. This superventilation naturally decreased the percentage of carbon dioxide in the alveolar air, but the blood returning to the lungs had a normal or slightly increased tension of carbon dioxide. In spite of this fact, his breathing was labored and fast, and he felt faint. This man was kept under observation for about a year and always gave the same result, save that he gradually developed a more severe bronchitis, together with asthma and emphysema, and finally was advised to go West to a dry climate.

We interpreted the disability in this case as being due to a dissociation between the ability of the blood to obtain oxygen and to rid itself of carbon dioxide. It was thought that the results indicated that the man was able to excrete his carbon dioxide without difficulty, but that he was unable to get enough oxygen. This condition was thought to be due to the presence of bubbles of foam in many of the alveoli, which prevented a free exchange of air while not preventing the free flow of blood through the pulmonary capillaries. The blood passing over these foam-filled alveoli was unventilated and reached the left ventricle in a venous condition. The superventilation present during exercise lowered the carbon dioxide tension in the alveolar air of the functional air sacs, and this blood was superventilated and contained a less than optimal amount of carbon dioxide but a normal amount of oxygen, since superventilation affects little if any the amount of oxygen the blood carries on leaving the lungs. The blood entering the left ventricle therefore would be a mixture of superventilated and underventilated blood. The mixture might have a normal carbon dioxide tension, but would have a subnormal oxygen tension. If the cardiac output were normal the blood returning to the lungs would have a normal carbon dioxide tension but a low oxygen content. In other words, there would be a dissociation between the ability of the blood to get rid of its carbon dioxide and to obtain its oxygen. This condition is analogous to that we have previously pointed out as existing in congenital heart disease, early pneumonias, and foreign bodies in one bronchus, and has been termed by us admixture cyanosis.

Experimental evidence that such a condition might be responsible for this case was found in an experiment performed with Dr. C. F. Hoover on a dog. A tampon made of lamb's wool was introduced into the bronchus of the animal, and the rate and depth of breathing, together with observations on the venosity of the blood, were recorded. It was found that blocking the bronchus of one lobe of the lungs resulted immediately in a quickened and deepened respiration, but in spite of this, blood drawn while the tampon was in place was venous in color. This color immediately disappeared when the tampon was removed. The blood could be made cyanotic or of normal color at will.

Unfortunately for the theory, no definite improvement in the man's condition was found when he was made to work while breathing high pressures of oxygen. In patients suffering from bronchial pneumonia, in which there is a large amount of moisture present, oxygen will relieve the cyanosis but will not affect the respiratory distress. The bubbles of air in the alveoli, being filled with

oxygen in this case, oxygenate the alveolar blood but do not decarbonize it; hence the respirations are little if any affected by this form of treatment. In spite of this fact if oxygen want is present in bronchial pneumonias, oxygen therapy is justified in these cases. The improvement in the condition of the cases cited by Barcroft and others, when gassed soldiers are made to breathe oxygen over long periods of time, may be due to an improvement in the tone of the tissues from the increased and more nearly normal oxygen tension of the blood bathing them.

In another case, that of Private R., who was sent to me through the kindness of Capt. F. P. Esselbruegge, of the Convalescent Station, Camp Meade, somewhat different results were obtained. This soldier had been gassed with phosgene and mustard on November 3. After a more or less normal convalescence, he was able to do the ordinary things of life, but found himself unable to exert himself without becoming dizzy and faint. His voice had been affected with mustard and he was unable to articulate well.

He was first seen by me at Camp Meade early in February, when he presented himself for physical examination after he had been marched hurriedly from the barracks to the examining room. He was pale with a bluish tinge, and almost fainted before we could seat him in a chair. On February 26, when he arrived at this hospital, he was able to do the ordinary things all right without discomfort, but any unusual exertion seemed to make him breathless and faint. He did not impress one as being ill, and physical examination was absolutely negative; there was no indication whatever of impairment of heart or lungs. We attempted to determine the nature of his disability by methods similar to those used in the case cited previously.

In these experiments the subject rested or exercised on a rowing machine; he respired through a mask fitted with Geer valves, and expired into a 100-liter spirometer, the excursion of each breath being recorded on a high vertical slow-moving drum. Each expiration was recorded as a vertical and somewhat diagonal line downward; each inspiration as a horizontal line. The stroke was timed by a pendulum and adjusted to give breathlessness at the end of a minute and a half. The number of strokes was recorded by an automatic counter on the machine, and the time determined by a stop watch. The subject seated himself on the rowing machine and at a signal began rowing. At the end of a half minute, one minute, and one minute and a half respectively, on separate tests, he was stopped abruptly and the carbon dioxide tension of the affluent blood of the lungs was determined by a method essentially the same in principle as used by Christiansen, Douglas and Haldane. This method will be described fully in the near future.

Control experiments were made on R.G.P. for comparison.

In the experiments shown in Table I, at the end of a minute Pvt. R. was distressed and complained of dizziness; at the end of a minute and a half he always complained of distress in his stomach, dizziness and shortness of breath. At the end of a minute, and of a minute and a half, it was interesting to note that the pressure of carbon dioxide in equilibrium with the affluent blood of the lungs was

TABLE I

FEB. 28, 1919. 10:00 A.M.				SUBJECT R. G. PEARCE
	Rest	½ Min.	1 Min.	1½ Min.
Strokes	0	20	40	60
Vol. of air respired	8.1 L.	20 L.	43 L.	69 L.
Corrected Vol. 0° and 760 Min.	7.3 "	18.4 "	37.5 "	60 "
Min. Vol. of air	7.3 "	36.8 "	37.5 "	40 "
Vol. rate per min. at the end of exercise	7.3 "	44 "	52.5 "	74 "
% CO_2 expired air	3.4%	3.7%	4.3%	4.7%
% CO_2 in equilibrium with affluent blood of lungs	7.1%	8.4%	10.4%	11.3%
O_2 absorbed for period	302 c.c.	645 c.c.	1520 c.c.	2800 c.c.
O_2 absorbed per minute	302 c.c.	1290 c.c.	1520 c.c.	1866 c.c.
Pulse rate	90	120	120	130 (irreg.)
Respiratory rate	16	40	40	40
Respiratory quotient	.82	1.05	1.06	1.02
FEB. 28, 1919.				SUBJECT PRIVATE R.
Strokes	0	17	39	54
Vol. of air respired	7.9 L.	21 L.	46 L.	87 L.
Corrected Vol. 0° & 760'	6.9 "	18.1 "	40.5 "	76 "
Minute Vol. of air	6.9 "	36.2 "	40.5 "	51 "
Vol. rate at end of exercise		45 "	60 "	90 "
% CO_2 expired air	3.2%	3.4%	3.6%	3.7%
% CO_2 in equilibrium with affluent blood of lungs	6.6%	8.3%	8.8%	9.5%
O_2 absorbed during period		560 c.c.	1700 c.c.	2800 c.c.
O_2 absorbed per minute	276 c.c.	1120 c.c.	1700 c.c.	1860 c.c.
Pulse rate	80	100	110	110
Respiratory rate per min.	21	46	46	54
Respiratory quotient	.92	1.1	8.6	1.05

not so high as in the case of R. G. P. If Pvt. R.'s limitation of work was determined because of impairment in the ventilatory membrane or because there was an insufficient minute volume of blood passing through the body per unit of time, it would be expected that the tension of carbon dioxide in the affluent blood of the lungs would be abnormally high, but such was not the case. The amount of work he was doing would not normally require a respiratory volume of 87 liters per minute. This is shown (1) by the comparatively low value of the carbon dioxide in the expired air, and (2) by the low value of the carbon dioxide in equilibrium with the affluent blood of the lungs as compared with normal controls; yet, in spite of this, he was cyanotic, dizzy, and in a state of collapse. This experiment suggests that there is some dissociation between the ability of this man to get rid of his carbon dioxide and to receive oxygen from the atmospheric air. Accordingly experiments were devised of a similar nature in which oxygen was breathed in place of air, as follows:

On March 3 Pvt. R. was supposed to row at the approximate rate of 30 strokes per minute, but failed to time himself properly with the pendulum. He was almost in collapse when he finished rowing, and he looked blue. He complained of being dizzy and of having a stomach ache. It was with reluctance that he consented to work again.

He repeated the experiment, but this time the spirometer from which he inspired had been filled with oxygen. When he finished he expressed surprise at the ease with which he had accomplished the work. His pulse rate was 20 beats

slower in this case than when air was breathed. He got up immediately and walked over to the faucet to get a drink of water. He was pink in color. The effect of oxygen in causing him to do a greater amount of work was too obvious to be disputed.

The experiment was repeated on R. G. P. In this case a faster rate of rowing was adopted. R. G. P. noted that there was a distinct feeling of comfort while working with oxygen, which was not the case when breathing air. The breaths were more easily taken and the feeling of fatigue following this very extreme exercise was much less. After the exercise with air breathing, the pulse rate was irregular and impossible to count on account of extra systoles. After oxygen breathing, the pulse rate immediately following the exercise was 125 and was free from extra systoles. The results are given in Table II.

TABLE II

MARCH 3, 1919.	AIR BREATHED		OXYGEN BREATHED	
	R. G. P.	Pvt. R.	R. G. P.	Pvt. R.
Time of observation	1′ 30″	1′ 30″	1′ 30″	1′ 30″
Total strokes	51	38	51	41
Vol. of air breathed liters at 0° and 760 min.	62	76.5	56	46.5
% CO_2 expired air	3.7	3.7	4.3	5.2
C.c. CO_2 expired	2300	2980	2400	2450

The marked effect in improving the respiratory picture noted in the case of Pvt. R. was not present in the case of R. G. P. The respiratory quotient was 1.025 for Pvt. R. and .87 for R. G. P. when breathing air. A respiratory quotient over 1. in this case means superventilation.

On the afternoon of March 6, 1919, another experiment was made on Pvt. R. in which he rowed on the rowing machine at the rate of 54 strokes in a minute and a half, in one case breathing air and in the other case breathing oxygen. Some adjustment of the valves in the apparatus had made the work of rowing and breathing somewhat easier than on former occasions. He also had the benefit of six days' exercise. He was in good spirits, and, as he said, feeling extremely well at the time of the experiment.

In the case of air breathing, he expired 77 liters in a minute and a half while making 54 strokes, and the percentage of carbon dioxide in the expired air was 3.7. On this occasion it was not possible to detect cyanosis. He complained of a pain in his side, but had no right heart dilatation as determined by Dr. Hoover.

After a half hour's rest he repeated the experiment, breathing oxygen in this case. He expired 57 liters of air while making 55 strokes in one minute and a half, and the percentage of carbon dioxide in the expired air was 5.2 per cent. He was less out of breath after this experience than on the former occasion, and said that he felt no ill effects whatsoever from the strenuous work; there was a marked difference in his action on the two occasions, although he was unaware of the fact that he had been breathing oxygen in one case and air in the other.

This experiment was repeated on R. G. P., who breathed 62 liters of oxy-

gen while making 54 strokes against 67 liters of air while doing the same amount of work. In the case of oxygen breathing, the expired air contained 5.2 per cent carbon dioxide; whereas it contained 4.8 per cent when air was breathed.

On March 10 a third experiment, similar to those of February 28 and March 6, was performed. In this case Pvt. R. breathed 60 liters of air in rowing one minute and a half, and at the end of this period the affluent blood of his lungs had a carbon dioxide tension in equilibrium with air containing 9 per cent of carbon dioxide. A half hour later he repeated the experiment but breathed oxygen. He breathed 52 liters in one minute and a half, and the carbon dioxide tension of the affluent blood of the lungs at the end of this period was 9.6 per cent, the expired air with air breathing containing 4.5 per cent and with oxygen 5.05 per cent carbon dioxide. On this occasion he said he was more out of breath when he was breathing oxygen than he was when breathing air, but that he performed the work very much more easily than he had at first. He had been required to take rather a large amount of exercise each day in making the tests we required of him, and in our opinion this exercise did him a considerable amount of good; in fact, we do not feel that he was very much below par in his ability to do work.

Inasmuch as Pvt. R. showed a marked increase in efficiency when breathing oxygen over that which he possessed when he was breathing air, it was suggested that we perform some experiments in which he was made to breathe atmospheres containing less than the normal amount of oxygen, in much the same way that aviators are tested in low atmospheres of oxygen by the rebreathing apparatus developed by Yandell Henderson in the aviation service U. S. A. He was able to breathe atmospheres containing 15 per cent of oxygen without any effect on the blood pressure or subjective sensations. The experiment was stopped because he looked blue. Blood counts and hemoglobin estimation showed nothing abnormal.

I can not find any explanation for Pvt. R.'s case. In the beginning, without question, the breathing of oxygen made it possible for him to work much more easily; but the effect soon wore off and he was able to do equally as hard work when breathing air. He received no treatment during his stay at the hospital save the exercise of running on a treadmill or rowing on the machine for brief periods. It is true, though, that he received much more strenuous exercise than he had ever received in camp. This exercise, which necessitated deep breathing, may have done much to relieve the irritation which possibly caused his distress. Oxygen want, due to unequal distribution of air in the lungs, producing an admixture cyanosis similar to that which we have shown may occur in pneumonia, may have been a contributing factor. His individual breaths, however, were too deep to suggest the presence of such a factor. The fact that the respiratory quotients are relatively low during the period of hyperpnea shows that he was keeping in respiratory equilibrium in spite of the abnormally deep ventilation. The improvement may have been simply the result of training and of some in-

crease in his confidence in his ability to work. I do not believe, however, that Pvt. R.'s case was a so-called neurosis.

The third case appeared to be one of the numerous neuroses which follow gassing. He was a well-built and well-nourished man of twenty-four. He had been slightly gassed and had been awarded some disability because of it. Respiratory studies failed to show anything abnormal in his case. We found that the suggestion that oxygen was being administered would cut his respiratory volume in half while doing an equal amount of work. When breathing what he believed was air, he would invariably superventilate his lungs and have a high respiratory quotient and a low pressure of carbon dioxide in the air in equilibrium with his venous blood. His sensations of dizziness were probably caused by the fact that, thinking he must breathe hard, he overdid the matter and washed out carbon dioxide to such an extent that he became dizzy.

CHEMICAL CHANGES IN THE BLOOD IN DISEASE*

I. Nonprotein and Urea Nitrogen

By Victor C. Myers, Ph.D., New York City

ALTHOUGH the nonprotein nitrogen normally constitutes only about one per cent of the total nitrogen of the blood, nevertheless greater interest is attached at the present time to variations in the bodies which form the nonprotein than the protein nitrogen. This is due largely to the fact that the variations in these nonprotein constituents give us an insight into some of the processes of anabolism and catabolism. The food nitrogen is carried by the blood to the various tissues and the waste nitrogen to the kidneys, directly or indirectly by the same medium. After a meal containing protein there is a temporary elevation in the nonprotein and amino nitrogen of the blood. In diseases of the kidney there may be at first only a slight rise in the uric acid or urea, although in the terminal stages of the disease there is generally a very marked elevation in all the forms of nonprotein nitrogen. The normal range of the various nonprotein nitrogenous components is given in Table I. Data are also included indicating the deviations which may occur in gout, interstitial and parenchymatous nephritis, and eclampsia.

Table I

Nonprotein Nitrogenous Constituents
Mg. to 100 c.c. of blood

CONSTITUENT	NORMAL	GOUT	EARLY INTERSTITIAL NEPHRITIS	TERMINAL INTERSTITIAL NEPHRITIS	PARENCHYMATOUS NEPHRITIS	ECLAMPSIA
				to		
Nonprotein N	25-30		30-50	350		
Urea N	12-15		12-30	300	30-60	10-25
Uric acid	2-3	4-10	3-10	25		
Creatinine	1-2		2-4	35		
Creatine	3-7			30		
Amino acid N	6-8			30	12	4-8
Ammonia N	0.1			1		

The figures for the normal creatine are taken from observations of Denis,[1] those for amino acid nitrogen from Bock,[2] except in the case of eclampsia , where observations of Losee and Van Slyke[3] the recorded. Other data are from our own observations.

The figures for ammonia are very small, but these figures may be taken as the maximal rather than the miminal values. In fact there appears to be some question at the present time as to whether ammonia actually exists in the blood.

The origin and rôle which the various nonprotein nitrogenous constituents play in metabolism, as well as the ease of kidney secretion, obviously greatly influence the content of these substances in the blood, both normally and pathologically. Folin's classic papers on the composition of urine published in 1905,[4] did much to give us a correct appreciation of the significance of the nitrogenous waste products which find their exit through the kidney. He pointed out that the

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urea and creatinine stood in marked contrast to each other, since the former was largely exogenous in origin, while the latter was almost entirely of endogenous formation. Uric acid stood in somewhat of an intermediate position, being about half endogenous and half exogenous under ordinary conditions of diet.

Regarding the formation of these compounds, the following brief statement may be made. Urea is formed largely in the liver from the ammonia resulting from the deaminization of amino acids set free in digestion, but not of immediate use to the animal organism. Uric acid originates as a result of the enzymatic transformation of the amino- and oxy-purines, in which various glands of the body participate. Creatinine would appear to be formed in the muscle tissue from creatine.

It is of interest to compare the partition of these nonprotein nitrogenous constituents in the blood with the similar partition in the urine. Upon the ordinary mixed diet their approximate distribution in the urine is 85 per cent urea N, 1.5 per cent uric acid N, 5 per cent creatinine N, 4 per cent ammonia N

TABLE II

COMPARATIVE NITROGEN PARTITION OF URINE AND BLOOD
In per cent of total nonprotein nitrogen

FLUID	URIC ACID N	UREA N	CREATININE N	AMMONIA N	REST N
Normal Urine	1.5	85	5	4	4.5
Normal Blood	2	50	2	0.3	46
Blood in Gout and Early Nephritis	6	50	2	0.3	42
Blood in Parenchymatous Nephritis (Nephrosis)	2	55	2	0.3	40
Blood in Terminal Interstitial Nephritis	2 to 3	75	2.5	0.5	20

and 4.5 per cent undetermined N. It is quite natural to expect a somewhat similar relationship in the nonprotein nitrogenous constituents of the blood. The table above discloses quite a different distribution, however. It will be noted that even in normal blood the percentage of uric acid nitrogen is greater, if anything, than in the urine, while the urea is definitely lower, the contrast with the uric acid in the case of the creatinine and ammonia being even more marked. As Folin and Denis[5] have pointed out, the human kidney removes the creatinine from the blood with remarkable ease and certainty, the completeness of the creatinine excretion being exceeded only by the still more complete removal of the ammonium salts. The striking difference between the ability to excrete uric acid on the one hand, and urea and creatinine on the other, is brought out from an examination of the normal concentration of the blood and urine. Judging from their comparative composition, the kidney normally concentrates the creatinine 100 times, the urea 80 times, but the uric acid only 20 times. As the permeability of the kidney is lowered in conditions of renal insufficiency, this becomes evident in the blood, first by a retention of uric acid, later by that of urea, and lastly by that of creatinine, indicating that creatinine is the most readily eliminated of these three nitrogenous waste products, and uric acid the most difficultly eliminated, with urea standing in an intermediate position.[6]

CLINICAL SIGNIFICANCE OF THE BLOOD UREA

Since urea is the chief component of the nonprotein nitrogen, and since its estimation is considerably simpler than that of the nonprotein nitrogen, our attention will be directed chiefly to the urea. Mosenthal and Hiller[7] have made a careful study of the relation of the urea to the nonprotein nitrogen in disease. They point out that the selective action of the kidney maintains the urea nitrogen at a level of 50 per cent or less of the total nonprotein nitrogen of the blood, but that an impairment of renal function, even of very slight degree, may result in an increase of the percentage of urea nitrogen. In advanced cases this may be even higher than the 75 per cent given in Table II.

To give a comparative idea of the values observed for urea nitrogen in various pathologic conditions, illustrative findings are given for a number of different conditions in Table III, the data being taken from actual cases. As will be noted, the conditions in which nitrogen retention may occur are quite

TABLE III

CONDITIONS WITH SIGNIFICANT UREA NITROGEN FINDINGS

CASE	URIC ACID	UREA N	CREATININ	DIAGNOSIS
	mg. to 100 c.c.			
1	15.0	240	33.3	Bichloride poisoning
2	4.5	75	8.5	Double polycystic kidney
3	14.3	263	22.2	Terminal chronic interstitial nephritis
4	9.5	25	2.5	Early chronic interstitial nephritis, died 3 years later
5	8.3	72	3.2	Chronic diffuse nephritis, syphilis
6	2.3	28	1.9	Chronic parenchymatous nephritis
7	11.4	106	6.1	Severe acute nephritis, recovery
8	...	50	2.5	Mild acute nephritis
9	9.7	58	3.3	General carcinomatosis
10	5.5	24	3.3	Carcinoma of larynx
11	9.0	46	2.9	Severe pneumonia, recovery
12	..	43	3.4	Syphilis
13	5.5	44	3.1	Intestinal obstruction
14	..	24	2.2	Gastric ulcer
15	3.3	20	2.9	Duodenal ulcer
16	7.2	18	2.5	Prostatic obstruction
17	..	14	2.0	Myocarditis
18	6.0	18	2.9	Diabetics of long standing
19	8.4	12	2.2	Gout

Strictly normal figures for urea nitrogen may be given as 12 to 15 mg. per 100 c.c. of blood, while figures above 20 mg. on the usual restricted diet of the hospital may be regarded as pathologic.[8]

numerous. Marked urea retention may occur not only in the terminal stages of chronic interstitial nephritis,* but also in such conditions as bichloride poisoning and double polycystic kidney, and in some cases of acute nephritis. In parenchymatous nephritis the findings are comparatively low. Relatively high figures are frequently noted in malignancy, pneumonia, intestinal obstruction, lead poisoning, and sometimes in syphilis and cardiac conditions, although in the last mentioned this may be due to renal complications. In uncomplicated cases of prostatic obstruction the findings do not appear to be much above 20 mg. urea nitrogen. A slight retention is frequently noted in gastric and duodenal ulcer, possibly for the same reason that retention is found in intestinal obstruction.

*For a more detailed discussion of the various factors concerned in some of the conditions, reference may be made to the papers of Farr and Austin,[9] and Tileston and Comfort.[10]

Advanced cases of diabetes frequently show definitely high figures, apparently due in some instances to the high protein diet, in others to a complicating nephritis. The fact that a normal urea is associated with a high uric acid is of practical value in cases of gout not complicated by nephritis. As indicated in Table I, the blood urea is only slightly elevated, if any, in eclampsia. In normal pregnancy, Folin[11] has noted that, strangely enough, the findings are subnormal, figures between 5 and 9 mg. having been observed.

Since urea is largely of exogenous origin, while creatinine is endogenous, it is subject to much greater variation, especially under dietary influences. It is of less prognostic value than the creatinine in advanced cases of nephritis, but a much better guide as to the value of the treatment. In cases of prostatic obstruction[12] the urea is an excellent preoperative prognostic test, much better than the creatinine, for the reason that cases showing creatinine retention already show sufficient urea retention to make them very poor risks. The renal factor can be disregarded when the urea nitrogen is 20 mg. or under, the patient operated on with caution between 20 and 30, while with figures over 30 the outlook is unfavorable. Nephritis in children[13] does not so quickly result in urea retention as in the adult. On this account it is an especially helpful prognostic test in the nephritis occurring in early life.

In conditions showing nitrogen retention there are obviously two lines of attack, (1) to increase the output of the kidneys and (2) to decrease the nitrogen intake, while still maintaining the caloric and other needs of the body. Until quite recently, the first method is the one that has been employed clinically, particularly with the use of such diuretic drugs as the theobromine-sodium salicylate. For some time it has been recognized that in acute cases such drugs were contraindicated, and Christian[14] and his coworkers have further shown that these drugs are of very doubtful value in chronic cases. However, as Foster and Davis[15] have pointed out, some increase in the nitrogen output may be obtained by increasing the fluid intake. That a reduction in the nitrogen intake will reduce the blood retention has been definitely demonstrated, and this is a rational form of treatment which may be employed in almost all cases. In 1913 Goodall[16] reported observations on the favorable influence of a protein-free diet (Folin's starch and cream diet) in chronic nephritis. He found that such a diet could be continuously maintained for periods of from 5 to 10 days without harm to the patient, and further, that such a restriction could be followed by a low protein diet for a considerable period of time, even in advanced cases, without a return of the disagreeable symptoms. Later, Folin, Denis, and Seymour[17] conclusively proved that lowering the level of protein metabolism served to reduce the nonprotein and urea nitrogen of the blood in mild cases of chronic interstitial nephritis. Three years later the dietary end of this treatment was considered somewhat more in detail by Chace and Rose[18] in the wards and laboratory of this hospital. A number of different menus were outlined, the first two of which are given in Table IV. Obviously neither of these should be continued for an extended period.

To illustrate how a reduction in protein intake will lower the urea nitrogen, even in a very severe case of chronic interstitial nephritis, data on J. B. are given in Table V below. Despite the fact that the (endogenous) creatinine could

TABLE IV

TWO DIETS FOR CASES OF SEVERE NEPHRITIS

Juice from 1 lemon,
2/3 cup water,
6 tablespoon lactose,
1 tablespoon cane sugar.
Served 4 times a day
Calories, 1,424 Ash alkaline Iron, 0.8 mg.

MORNING		NOON		EVENING	
Banana	300 gm.	Cream soup	200 c.c.	Banana	300 gm.
Cream	100 c.c.	Banana	300 gm.	Cream	100 c.c.
Cocoa	200 c.c.	Milk	200 c.c.	Cocoa	200 c.c.

Calories, 1,585 Protein, 35.4 gm. Ash, alkaline, 15.6 N Iron, negl.

TABLE V

CASE (J. B.) ILLUSTRATING THE INFLUENCE OF A LOW PROTEIN DIET ON UREA NITROGEN IN CHRONIC INTERSTITIAL NEPHRITIS

DATE 1917	URIC ACID	UREA N	CREATININE
	mg. to 100 c.c.	mg. to 100 c.c.	mg. to 100 c.c.
Jan. 5	....	135	9.7
Jan. 9	....	110	12.5
Jan. 16	....	93	9.5
Jan. 30	5.0	48	7.8
Feb. 16	5.4	56	9.1
Feb. 27	7.1	45	7.5
Mar. 6	6.1	49	6.4
Mar. 23	....	40	7.7
Apr. 13	5.9	46	6.4
Apr. 27	....	45	7.5
May 15	....	33	7.3
May 22	....	24	7.3
June 5	....	34	6.7
July 17	....	29	6.8

Patient left hospital clinically improved on June 9, returned to work as guard on the subway, but died Nov. 7, 1917.

not be appreciably lowered, the urea nitrogen gradually fell to a level not more than twice the normal.

Some workers have endeavored to obtain more definite information than the blood alone will give regarding the ability of the kidneys to excrete urea, by comparing the urinary excretion with the concentration in the blood. Attention has been given to this particularly by Ambard[19] in France and McLean[20] in this country, who have worked out formulæ to express this relationship. Our own experience with this method has been disappointing in that the results have failed to reveal any added information not given by the blood alone.[21] We have long felt what Folin[11] has recently stated; viz., "The complicated mathematical formulas introduced in connection with the Ambard coefficient do not tend to increase one's confidence in that coefficient. It is difficult to see how square roots and cube roots help to elucidate such a simple metabolism proposition."

During the past year Van Slyke has made an effort to derive a formula which would correctly express the various factors involved, although so far this work has been reported only in a preliminary way.[22]

Obviously if this method of studying the urea excretion is used, it is essential that accurate collections of urine be made for the 60 or 72 minute specimen

employed. This can be done if sufficient attention is given to the matter, but practically it seems difficult of execution in most hospitals.

METHOD OF TAKING BLOOD SPECIMENS

For most chemical analyses, blood can best be prevented from clotting by the addition of potassium oxalate. The potassium salt is much to be preferred over the sodium salt on account of its greater solubility. In case it is desired to analyze the plasma instead of the whole blood, this may readily be obtained by centrifuging the specimen. Our method has been to add 2 to 4 drops of 20 per cent potassium oxalate to large neck bottles of about 35 c.c. capacity, and then thoroughly dry these bottles in a hot air oven at a temperature sufficiently high to practically sterilize them. This insures a uniform amount of oxalate in the bottle* in a fairly divided state. The blood should be drawn directly into the bottle and at once gently but thoroughly mixed with the oxalate by rotating the bottle. Occasionally it may be found desirable to draw the blood into a syringe, the barrel of which may be moistened with the oxalate solution.

It is quite essential that specimens be secured under as uniform conditions as possible. Fairly constant conditions are obtained by taking the blood in the morning before breakfast, i. e., after a 12 to 14 hour fast and before any food or fluid has been taken. If dietary treatment is to be instituted (as in cases of gout, nephritis, and diabetes) to be especially helpful, the first specimen taken must precede these dietary restrictions in order that they may give a reliable indication of the influence of the treatment.

The question sometimes arises, how long can a specimen of blood be kept and have the analysis valid. If possible, specimens should always be analyzed the same day they are taken. Where good refrigeration is available, however, specimens can frequently be kept for several days without apparent serious deterioration, but this statement does not apply to specimens sent by mail which are at room temperature for several days. When blood is taken in a sterile oxalated container it may be allowable for such specimens to be sent by mail when analysis is made in 24 hours. Personal experience has shown, however, that such bloods generally show low blood sugars, a very good indication that deterioration has already set in.

METHODS OF CHEMICAL BLOOD ANALYSIS

In hospital work chemical blood analyses are now made so frequently and in such large numbers that it is important that the various procedures should be as simple as possible. As a step in this direction, Folin and Wu[23] have recently devised a system of chemical blood analysis in which a large number of analyses are made on the same protein-free filtrate. With this scheme, it is possible to make very quickly a single or several fairly complete blood analyses. In a hospital laboratory, however, one is frequently called upon to make determinations of such substances as urea, sugar, etc., on a very large number of specimens of blood. The methods we are about to describe appear to fit this second scheme of work. Since this subject is still in its infancy, improvements in technic are

*Cummer[32] has recently described a device which may readily be adapted to this work.

almost a daily occurrence. Although chemical blood analysis methods are relatively simple, there are many pitfalls for individuals without suitable chemical training. A physician can not expect that his office girl or nurse can properly manipulate these methods without an appreciation of the chemical factors involved.

ESTIMATION OF NONPROTEIN NITROGEN

The use of acetone-free methyl alcohol was first suggested by Folin and Denis[24] as the protein precipitant in the nonprotein nitrogen estimation. With this precipitant, the results, as Greenwald has pointed out, are somewhat low for the reason that amino acids appear to be partly precipitated. Another objection to the use of methyl alcohol is that some lipoid nitrogen is included in the filtrate. On this account Greenwald[25] suggested the use of trichloracetic acid. Subsequently Folin and Denis[26] recommended the use of *m*-phosphoric acid, although in their system of blood analysis Folin and Wu[23] use tungstic acid. Folin[27] has stated that he prefers that precipitant which gives the lowest results without lowering the values of any known constituent.

After the removal of the protein constituents it is necessary in any case to carry out a micro-Kjeldahl digestion on the nonprotein nitrogenous material. The ammonia may then be aerated or distilled off and finally estimated either colorimetrically with Nessler's solution or titrated with the aid of 0.01 N acid and alkali. In the recent method of Folin and Wu the digested material is nesslerized directly.

We have found the trichloracetic acid precipitation of Greenwald very satisfactory, although as a protein precipitant, it is mechanically hardly the equal of Folin and Wu's tungstic acid. After aeration we have carried out the final estimation colorimetrically as originally suggested by Folin and Denis.

Method.—Three c.c. of blood are diluted to ten times the volume (30 c.c.) with 5 per cent trichloracetic acid solution. After thorough mixing, it is allowed to stand for thirty minutes, then filtered. With the above treatment sufficient filtrate is generally obtained (20 c.c.) so that duplicate determinations may be made if desired. (In case one prefers the tungstic acid precipitation, the technic of this may be found under the clinical estimation of urea with the Myers' colorimeter, omitting, of course, the urease for this purpose.)

Into a thin glass test tube about 150 mm. in length and of diameter (20 mm.) such that it will readily slip into a 100 c.c. cylinder, are pipetted 10 c.c. of the filtrate, the equivalent of 1 c.c. of blood. Approximately 0.2 gm. of potassium sulphate, 2 drops of 10 per cent copper sulphate solution and 0.3 to 0.5 c.c. of conc. sulphuric acid, all of the highest purity reagents (nitrogen-free), are added and the mixture boiled over a small microburner flame, first gently (to remove the water) and then until digestion is complete, i. e., two minutes after the mixture becomes colorless. The final oxidation may be greatly facilitated by the addition of 1 or 2 drops of hydrogen peroxide. The tube is allowed to cool for a couple of minutes and then about 6 c.c. of distilled water added.

Aeration of the ammonia may be conveniently carried out in the apparatus* (Fig. 1), described by the writer in 1914.[28] This apparatus has two important advantages over that

*This aeration apparatus may be very simply constructed provided 100 c.c. cylinders without lips are available. The holes in the ends of aeration tubes, as Folin has pointed out, may readily be made with a platinum wire which is at white heat, provided the glass is only moderately hot. Malleable iron wire works quite as well as the platinum. The cylinders or the apparatus complete may be obtained from the C. M. Sorensen Co., Inc., New York City.

originally suggested by Folin and Denis for this purpose; first, it is not necessary to insert a stopper into a fragile test tube, and second, nesslerization is carried out directly in the second cylinder, which allows a wide range of dilution in contrast to the fixed dilution of a volumetric flask. (The aeration of the ammonia from the urea, described below, is carried out with the same apparatus.)

Into a 100 c.c. graduated cylinder without lip are added 15 c.c. of distilled water and 2 c.c. of 0.1 N hydrochloric acid or 2 to 3 drops of the 10 per cent solution. This is now closed with a two-hole stopper having a glass tube passing nearly to the bottom of the cylinder. The tube is sealed at the lower end, but contains a number of small holes to aid in the complete absorption of the ammonia. The apparatus to connect the pair of cylinders is adjusted, the test tube containing the digested mixture placed in the ungraduated cylinder, 3 c.c. of saturated sodium hydroxide carefully allowed to run down the side of the tube and to the bottom of the acid solution and the stopper quickly inserted. The cylinder containing the digested mixture is connected with a wash bottle containing dilute sulphuric acid so that the incoming air will be completely ammonia-free. The outlet tube in the graduated cylinder is now connected with a suction pump and air slowly allowed to pass through the apparatus, the speed being increased so that at the end of two minutes the air current is as rapid as the apparatus will stand. A series of a half-dozen or more tubes may conveniently be set up in this way. Aeration is complete in 10 to 30 minutes and the apparatus is then disconnected.

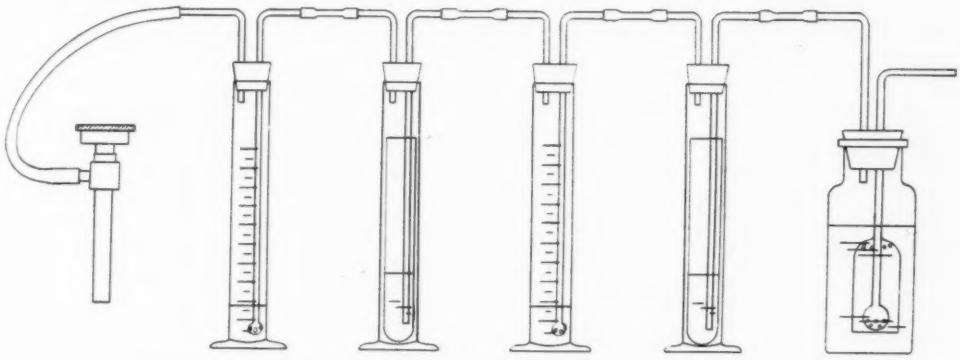

Fig. 1.—Aeration apparatus for nonprotein and urea nitrogen estimation.

Into a volumetric flask of 100 c.c. capacity are pipetted 5 c.c. of ammonium sulphate solution* containing 1 mg. of nitrogen and 50 to 60 c.c. of distilled water are added. Sufficient of the modified Nessler's solution** for the standard and the unknown is diluted about five times with distilled water, and of this about 20 c.c. added to the standard solution, which is then made up to the mark with water. At the same time 7 to 8 c.c. of freshly diluted Nessler's solution are added to the unknown and the volume made up to 25 c.c. in the graduate, unless a high content of nonprotein nitrogen is indicated, in which case more Nessler's solution (up to 25 c.c.) and a dilution to 35, 50, 100 c.c. or even more may be

*A standard solution containing 1 mg. of N per 5 c.c. of solution may be prepared by dissolving 0.944 gm. ammonium sulphate or 0.764 gm. ammonium chloride of the highest purity in distilled water and making up to 1,000 c.c.

**Modified Nessler's Solution (Bock and Benedict Formula).—Place 100 gm. mercuric iodide and 70 gm. potassium iodide in a liter volumetric flask and add about 400 c.c. of water. Rotate until solution is complete. Now dissolve 100 gm. sodium hydroxide in about 500 c.c. water, cool thoroughly, and add with constant shaking to the mixture in the flask; then make up with water to the liter mark. This usually becomes perfectly clear. When the small amount of dark brownish red precipitate, which forms, settles out, the supernatant fluid is ready to be poured off and used.

When pure mercuric iodide can not be obtained Folin and Wu have pointed out that metallic mercury and iodine may be substituted. To 75 gm. of potassium iodide and 55 gm. iodine in a 500 c.c. flask add 50 c.c. of water and an excess of metallic mercury, 75 gm. Shake the flask for 7 to 15 minutes or until the dissolved iodine has nearly disappeared. When the red iodine solution has begun to become visibly pale, though still red, cool in running water and continue the shaking until the reddish color of the iodine has been replaced by the greenish color of the double iodide. Now separate the solution from the surplus mercury by decantation and washing with about 400 c.c. of distilled water. Add 500 c.c. of water containing 100 gm. of sodium hydroxide as in the first formula and make up to 1 liter.

needed to make the color of the unknown approximately the same intensity as the standard. This is usually set at the 15 or 20 mm. mark on the colorimeter (Bock-Benedict, Duboscq or Kober). The colors are now matched up, preferably with the aid of a north light.

The following formula may be used for the calculation (applies to all three colorimeters), $\frac{S}{R} \times \frac{X}{100} 1 \times 100 =$ mg. nonprotein N to 100 c.c. of blood in which S represents the depth of standard, R the reading of the unknown, X the dilution of the unknown, 100 the dilution of the standard, 1 the strength of the standard in mg. and 100 the factor to convert the result to mg. per 100 c.c., since the equivalent of 1 c.c. of blood was employed.

ESTIMATION OF UREA NITROGEN

The method for the estimation of urea nitrogen is one that we have constantly employed for the past seven years,[6,27] and although other methods have been tried from time to time, none has been found as expeditious or as satisfactory. With a good preparation of urease the results obtained in the estimation of urea are perhaps the most reliable of any of the chemical blood determinations. The method is based on suggestions of Marshall,[29] of Van Slyke[30] and of Folin.[31]

The apparatus employed for the urea nitrogen estimation is the same as for the nonprotein nitrogen and if desired the two determinations may be run at the same time.

Method.—Into a test tube of the same size as that employed for the nonprotein nitrogen are introduced 1 c.c. of a 5 per cent jack bean urease solution.* Two c.c. of the oxalated blood are now added, preferably with an Ostwald-Folin pipette and the tube (or series of tubes) incubated in a beaker of water at 50° C. for 15 minutes. At the end of this time the aeration apparatus is put in order, 1 to 2 c.c. of amyl alcohol (or 4 to 5 drops of pure caprylic alcohol) are added and then about 4 to 5 c.c. of saturated carbonate. The tube is at once inserted in the ungraduated cylinder, the stopper replaced and aeration carried out for about 30 minutes, the air current being allowed to run slowly at first, but later as rapidly as the apparatus will stand.

The development of the color and comparison in the colorimeter is carried out just as described above, but in making the calculation it should be borne in mind that 2 c.c. of blood have been employed. If it is desired to convert the urea nitrogen into terms of urea, this may be done by multiplying by the factor 2.14.

Where only an occasional estimation of urea is carried out, the aeration procedure may appear a little troublesome. In an attempt to simplify this step we have tried a number of different protein precipitants, but in no case have the results been quite as satisfactory as with aeration. We originally suggested the use of heat and acetic acid together with colloidal iron, but later abandoned this in favor of *m*-phosphoric acid. Picric acid, and a weak acetic acid solution of potassium mercuric iodide were also tried, but recently Folin and Wu's tungstic acid has been employed. This reagent is quite the best protein precipitant that we have used in this connection.

*Concentrated preparations of jack bean urease may be obtained on the market (Arlington, Squibb), prepared according to the Van Slyke formula. Folin has pointed out that the keeping power of these preparations is not constant, although we never experienced difficulty with them until quite recently. Folin and Wu suggest the following method of preparation: "Transfer to a 200 c.c. flask about 3 gm. of permutit powder. Wash this by decantation, once with 2 per cent acetic acid, then twice with water. Add to the moist permutit in the flask 100 c.c. of 30 per cent alcohol (35 c.c. of 95 per cent alcohol mixed with 70 c.c. of water). Then introduce 5 gm. jack bean meal (may be obtained from the Arlington Chemical Co.) and shake for 10 minutes. Filter and collect the filtrate in three or four different small clean bottles. Set one aside for immediate use; it will remain serviceable at least 1 week at ordinary room temperature, if not exposed to direct sunlight. Put the others on ice where they will remain good for 3 to 5 weeks."

The blood is digested in the usual way and then diluted 1 to 10 with water and the precipitation reagents. After filtration 5 c.c. of the diluted Nessler's solution are added to 5 c.c. of the filtrate (the equivalent of 0.5 c.c. of blood) and color comparison made in the usual way. Turbidity seldom develops. The results compare favorably with those obtained by the aeration method.

The technic of the method is described below in connection with the simple test tube colorimeter illustrated.

Method.—Into a large test tube (160 × 25 mm.) are introduced 1 c.c. of 5 per cent urease solution or about 0.1 gm. of the dry enzyme. With an Ostwald-Folin pipette 2 c.c. of the oxalate blood (or 1 c.c. if a large amount of urea is anticipated) are now added and the tube incubated in a beaker of water at 50° C. for 10-15 minutes. At the end of this time 14 c.c. (or 15 c.c.) of water are added and 2 c.c. of 10 per cent sodium tungstate, and then while rotating the tube, 2 c.c. of 2/3 N sulphuric acid. Shake vigorously. When a

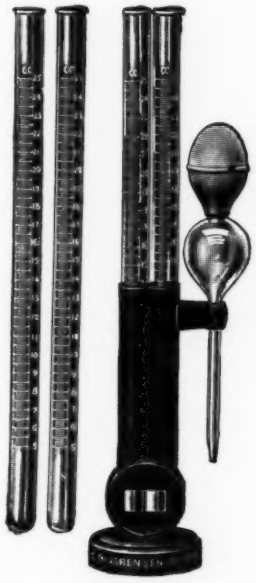

Fig. 2.—Test tube colorimeter.

blood is properly coagulated, the color of the coagulum turns from pink to dark brown. If this change does not occur, the coagulation is incomplete due probably to too much oxalate. In such a case 5 per cent sulphuric acid may be added, a drop at a time, shaking between each addition until the coagulation is complete. If the mixture is now carefully poured upon the double portion of a filter paper just large enough to hold the mixture the filtrate will usually come through perfectly clear, if not, the first portion may be returned to the filter.

Into the left-hand tube of the colorimeter are pipetted 5 c.c. of ammonium sulphate or ammonium chloride solution, containing 0.1 mg. of nitrogen. Two or three c.c. of modified Nessler's solution are now diluted about five times with distilled water to the 10 c.c. mark. This gives a standard 1 mg. N to 100 c.c. in strength. If 0.5 mg. to 100 c.c. dilution is desired, as is generally the case with normal blood, dilute to 20 c.c. with distilled water.

Five c.c. of the blood filtrate are pipetted into the right-hand tube of the instrument and 3-4 c.c. of the diluted Nessler's solution added. (This should be done nearly simultaneously with the addition of the Nessler's to the standard.) The solution should be per-

fectly clear. Dilution is now made with distilled water, inverting after each addition, until the depth of color is identical with the standard (1 or 0.5 mg. to 100).

For the calculation of the urea nitrogen, the following formula may be employed in which "S" represents the standard and "R" the dilution of the unknown: $\frac{100}{S} \times R \times 200 =$ mg. urea N per 100 c.c. of blood. Since the 5 c.c. of the filtrate employed are the equivalent of 0.5 c.c. of blood, it is obviously necessary to multiply by 200 to obtain the mg. of urea nitrogen per 100 c.c. of blood. With the 0.5 mg. standard and a dilution of 15 c.c. for the unknown the formula would work out as follows: $\frac{0.5}{100} \times 15 \times 200 = 15$ mg. urea N. That is with this scheme the dilution of the unknown gives the mg. urea nitrogen directly.

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THE HISTOGENESIS OF CARCINOMA IN THE ISLETS OF THE PANCREAS

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THE earliest stages of carcinoma have been found in association with chronic inflammatory changes in many organs of the body; therefore it seemed theoretically possible that similar neoplastic changes might be found in association with chronic pancreatitis. With this idea in mind I examined two hundred and sixty-two pancreases which were removed at necropsy from patients who died with ulcer of the stomach, ulcer of the duodenum, cholecystitis with and without stones, cholangitis with and without stones, and carcinoma of the stomach, liver, gall bladder, and bile ducts. In no case in this series was a definite advanced carcinoma of the pancreas studied, although comparison was made of thirty-six specimens of tissue from late carcinoma with the tissue showing early changes.

In the cases available for study the pathologic condition of the pancreas found in association with those chronic upper abdominal lesions mentioned were acute and chronic pancreatitis, stages of fat necrosis, simple cysts, cyst adenomas, papillary cystadenomas, hypertrophy and hyperplasia in the islets of Langerhans. Of these conditions, hypertrophy and hyperplasia in the islets in chronic pancreatitis were selected as the object of this special investigation. In order to obtain more accurate knowledge which might throw light on the histogenesis of carcinoma of the pancreas, a detailed study of pathologic specimens, grossly and microscopically, was made. This was supplemented by the study of the normal development and structure of the pancreas.

EMBRYOLOGY

The pancreas in man develops from two anlages which appear in the embryo of 3 to 4 mm. in length. The dorsal pancreatic anlage begins as an outpouching on the duodenum, the ventral pancreatic anlage as a grooved bud arising from the common bile duct (Fig. 1). The growth of the dorsal pancreas is more rapid than that of the ventral. The anlages grow separately until they meet posterior to the duodenum where they coalesce and continue development in one mass in the dorsal mesentery. The body and tail grow upward and to the left to lie in the dorsal mesogastrium posterior to the stomach. As the stomach and dorsal mesogastrium change position the pancreas moves within the dorsal mesogastrium until its position is transverse when it becomes firmly fixed to the parietal peritoneum of the posterior abdominal wall. In one embryo,† 26 mm., which I studied, the dorsal and ventral anlages are fused.

The primitive outpouchings are lined with a columnar epithelium similar to that in the duodenum. As the buds grow the epithelium develops branching ducts

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†University of Minnesota, Collection No. H29.

ramifying the connective tissue. The main duct of the dorsal pancreas opens into the duodenum while the main duct of the ventral pancreas opens into the common bile duct at the ampulla. When the dorsal and ventral anlages unite, the main duct of the ventral pancreas makes a lateral anastomosis into the main duct of the dorsal pancreas. In this way the main duct of the ventral pancreas with the distal half of the duct of the dorsal pancreas forms the duct of Wirsung, and the proximal half of the duct of the dorsal pancreas is the duct of Santorini. When the embryo is from 26 mm. to 33 mm. in length, and the tail of the pancreas extends well out into the dorsal mesogastrium, branching tubules can be seen throughout the gland. No acini or islets are to be seen at this stage, and there is no evidence of lobulations. The connective tissue forms the major portion of the organ. At the end of the branches of the main duct the tubules have an enlarged bud. This bud branches and forms new tubules until the acini begin to form by several buds at the tip of each tubule. After the acini have begun to form throughout the gland the islet cells appear in the connective tissue along the

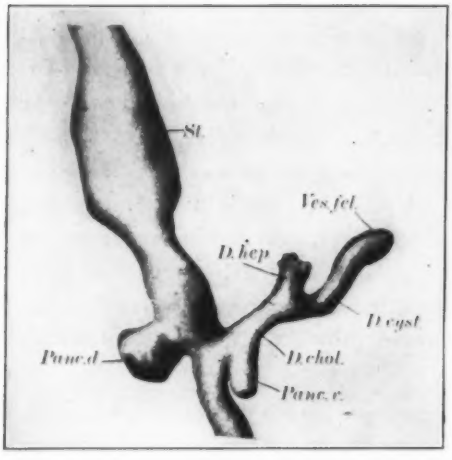

Fig. 1.—Reconstruction from a human embryo at 7.5 mm. (H.E.C. 256). x55 diams. *D. chol.*, ductus choledochus. *D. cyst.*, ductus cysticus. *D. hep.*, ductus hepaticus. *Panc. d.*, pancreas dorsale. *Panc. v.*, pancreas ventrale. *St.*, stomach. *Ves. fel.*, vesica fellea. (Thyng.)

Fig. 2.—(H187 Univ. of Minn. Collection) Microphotograph of pancreas in embryo (158 mm. C. R. Length) showing relation to stomach and left adrenal.

small ducts. Pearce found masses of cells which he identified as islet cells in an embryo of 54 mm. In the section of one embryo,* 158 mm. in length, in which I examined the ducts, acini and islets were well developed. The islets stand out clearly in the loose connective tissue near the ducts. They are circular masses, the cells of which are not well differentiated. As the glandular tissue grows into the connective tissue it envelops the islets. The connective tissue is derived from the mesodermal tissue of the dorsal mesentery (Fig. 2).

HISTOLOGY

The embryology of the pancreas has been sufficiently studied in man and in species of lower vertebrates to establish the fact that all the histologic units develop from the same anlages.

*University of Minnesota, Collection No. H29.

The pancreas is a "mixed" epithelial gland composed of three separate and distinct histologic units each made up of differentiated, specialized epithelial cells:

1. The pancreatic ducts (of Wirsung, Santorini, the interlobar and intralobular ducts, and the anastomosing tubules of Bensley).
2. The alveolar glands.
3. The islets of Langerhans (Fig. 3).

The Pancreatic Duct System.—The duct system in the pancreas is made up of one large duct, the duct of Wirsung, and an accessory duct, the duct of Santorini. From these ducts numerous highly branched tubules ramify the organ. The duct of Wirsung passes from the duodenal portion of the organ, where it opens into the ampulla of Vater, to the splenic portion. Throughout its entire length the first division of the tubules opens into it. These primary branches do not enter directly; they pass obliquely through the connective tissue of the duct of Wirsung for a short distance. The terminal branches are rather tortuous;

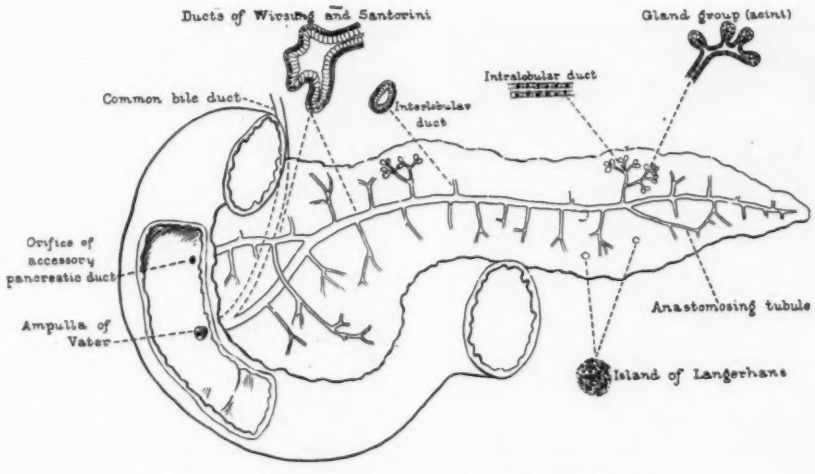

Fig. 3.—Diagram of pancreas showing its histologic units.

Bensley has shown that they have many anastomosing tubules. The main ducts (Wirsung and Santorini) are lined with a single layer of high columnar epithelium on a fine membrana propria; in some sections it is thrown up into folds. In the interlobular and intralobular and anastomosing tubules the epithelium is a single layer of columnar cells, gradually diminishing in height in the terminal branches.

The Alveolar Glands.—Projecting out from the terminal ends of the tubules are the alveolar glands. These are branched tubular glands lined with a single layer of large secreting cells, pyramidal in shape, the apex of which points into the lumen of the acinus; the base, near which is a large circular nucleus, lies on a membrana propria. The cytoplasm is divided into two zones, granular and homogeneous; the granular zone at the apex is made up of the zymogen granules in a faintly staining protoplasm; the homogeneous zone is in the basal portion of the cell. The zymogen granules in the granular layer and the mitochondrial filaments in the homogeneous layer may be studied only by the use of special fixation

and staining. The secreting acinic cells receive their blood supply from a capillary network in the membrana propria.

The Islets of Langerhans.—These islets are small circumscribed masses of epithelial cells distributed throughout the entire organ, although they are more numerous in the splenic portion. Most of the islets are spherical, from 0.2 to 0.3 mm. in diameter, but they may be oval in shape. They have no duct connection, either with the pancreatic tubules or with each other, but lie in close relationship to the tubules. The texture of the connective tissue separating them from the acini is very delicate. The arteries supplying the islets form a rich capillary cluster. The vessels do not enter through a hilus. Each islet has a number of small capillaries which pass in from the connective tissue at different points on the surface. The arrangement of the efferent blood stream is the reverse.

The islet cells are of two varieties, A and B. The A cells are the larger; they have a large elliptical nucleus with the chromatin in one or two round

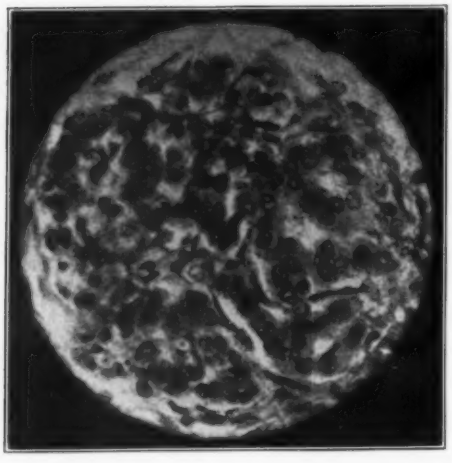

Fig. 4.—(H187 Univ. of Minn. Collection) Microphotograph of islet in embryo pancreas.

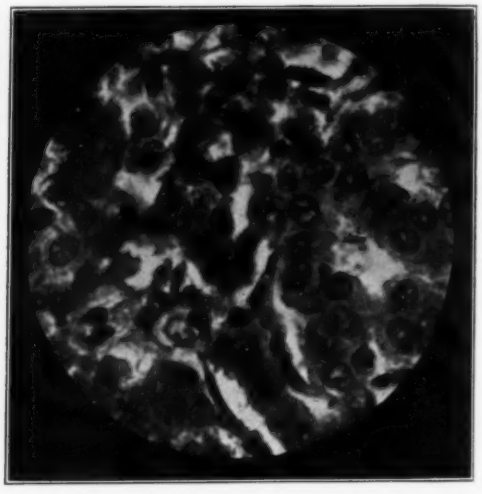

Fig. 5.—(H187 Univ. of Minn. Collection) Oil immersion microphotograph of islet cells, embryo 158 mm.

clumps. In the cytoplasm there are many small granules. The smaller B cells are more numerous; they have a central nucleus which is circular and contains a larger amount of chromatin. Their cytoplasm is packed with small granules. These cells may be differentiated from one another and the granules stained only by the fixation and staining methods of Lane. In the sections the cells are seen in irregular masses, in single, or in double cords. They lie in a delicate connective tissue among the loops of the capillary cluster (Figs. 4, 5, 6, 7, 8, and 9).

Blood Vessels.—The blood supply to the pancreas is through the splenic, hepatic, and superior mesenteric arteries. The main trunk of the splenic and hepatic arteries each sends a number of branches. The superior pancreaticoduodenal and the inferior pancreaticoduodenal supply the head with a number of branches. The veins which are tributaries of the portal system follow the arteries.

Lymphatics.—The lymphatics drain into the splenic, anterior, and posterior pancreaticoduodenal groups (Fig. 10).

PATHOLOGY

Technic.—The pancreatic tissue was examined grossly; blocks cut from the duodenal, central, and splenic portions of the pancreas were sectioned and stained for microscopic study. The gross specimens had been preserved in neutral 10 per cent formalin solution. Blocks for microscopic study are preserved in 10 per cent formalin solution, Zenker's fluid with acetic acid, and Bensley's formalin-

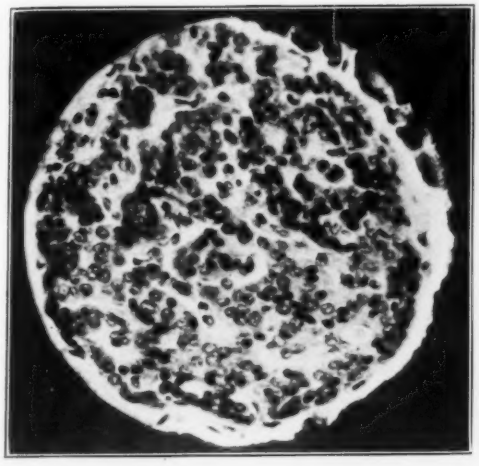

Fig. 6.—(A135776). Microphotograph of islet in an infant aged eight months.

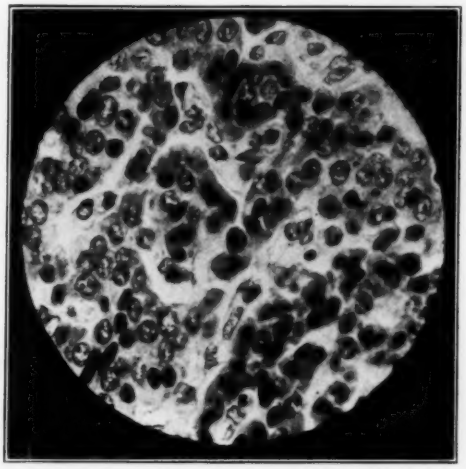

Fig. 7.—(A135776). Oil immersion microphotograph of islet cells in an infant aged eight months.

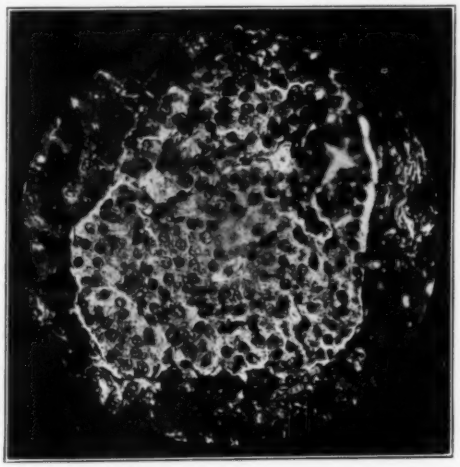

Fig. 8.—(A122722). Microphotograph of islet in pancreas of adult.

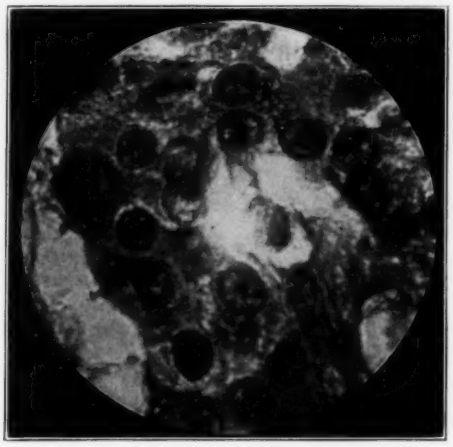

Fig. 9.—(A122722). Oil immersion microphotograph of islet in pancreas of adult.

Zenker solution. Blocks from all the specimens which are preserved in formaldehyde solution were placed in a weak aqueous solution of ammonia for twenty-four hours and a few drops of strong ammonia added to the weaker alcohols when the tissues were being dehydrated; those preserved in Zenker's fluid with acetic acid and Bensley's formalin-Zenker were dehydrated in the usual manner. The blocks were embedded in paraffin and several slides from each

block were cut in series for the routine microscopic examination. Additional blocks and sections were cut when needed. A few frozen sections were made. Some sections were stained with Ehrlich's hematoxylin and eosin and Goodpasture's acid polychrome-methylene blue and eosin. Others were stained with phosphotungstic acid hematoxylin and Bensley's brasiline water blue to differentiate the islet epithelium from the acinic epithelium. The blocks of tissue which had been preserved in formaldehyde and treated with ammonia could be differentiated by these stains also.

Chronic Pancreatitis.—Chronic pancreatitis is an almost if not a constant finding in association with gastric and duodenal ulcer; it is most marked, however, in the duodenal portion of the organ. The amount of pancreatic involvement and the degree of inflammatory reaction are dependent on the location and duration of the ulcer and the severity of the acute exacerbations. When the

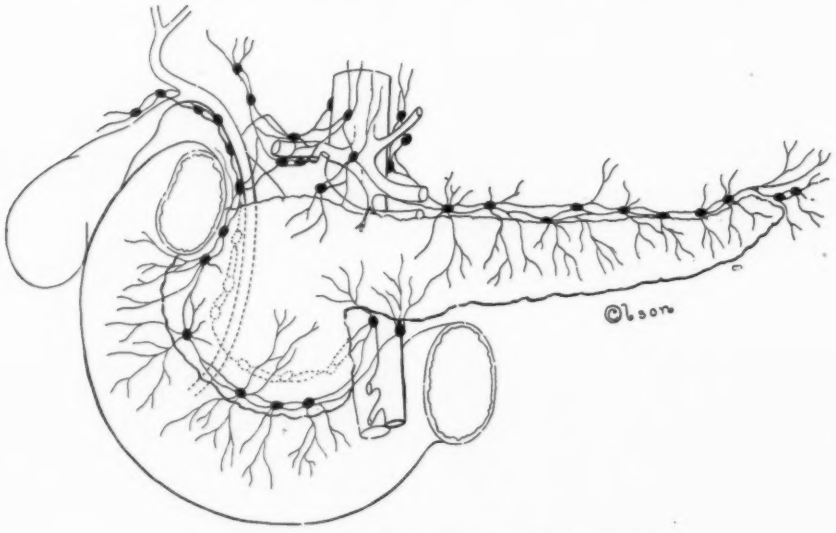

Fig. 10.—Diagram of peripancreatic lymphatic glands.

gastric or duodenal ulcer perforates on to the pancreas and an area of the pancreas becomes the base of the ulcer the marked local pancreatitis which develops gradually changes from an acute to a chronic form (Fig. 11). In addition there is usually a diffuse pancreatitis (Figs. 12 and 13). The pancreatitis is manifested either by a lymphocytic infiltration or by fibrosis extending into the interlobular, interacinar and periductal connective tissue.

Hypertrophy of the Islets Observed in the Series of Cases Studied.—In the microscopic examination of sections of the pancreas from the 262 cases that were selected for this study, hypertrophy of the islets in connection with a chronic pancreatitis was found in 48 cases. When the histories of these 48 cases were examined, two important discoveries were made; first, none of them showed glycosuria in any of the urinalyses of twenty-four hour specimens made while the patients were under observation and examination; second, 79.3 per cent of these were found to be cases in which a gastric or duodenal ulcer was found at operation or at necropsy. In the series of 262 cases which was selected

for this study gastric ulcer was found in 71; in seventeen (25 per cent) the islets showed hypertrophy. Duodenal ulcer was found in 61 cases; in nineteen (31 per cent) the islets showed hypertrophy. Gastric and duodenal ulcer were found associated in 11 cases; in two (18.1 per cent) the islets showed hypertrophy. Hypertrophy of the islets was also observed in 6 cases of gastric carcinoma, 2 cases of carcinoma of the rectum, one case of carcinoma of the sigmoid, and 1 case of cyst of the pancreas.

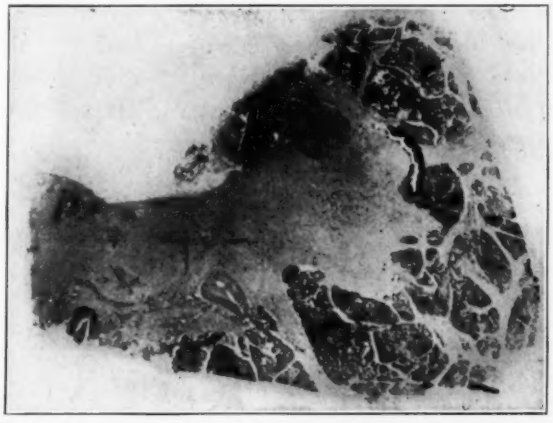

Fig. 11.—(A36163). Microphotograph of duodenal ulcer perforated onto pancreas, showing marked connective tissue reaction in area of localized pancreatitis.

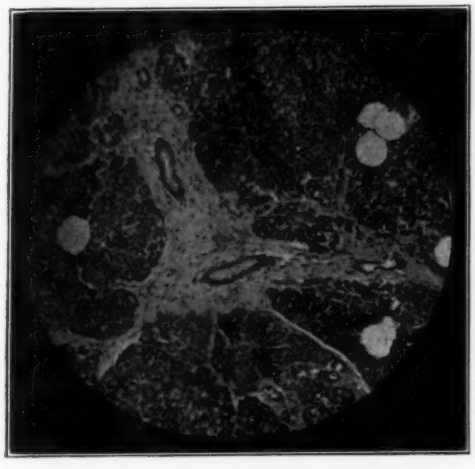

Fig. 12.—(A61333). Microphotograph. Chronic pancreatitis. Interlobular fibrosis most marked.

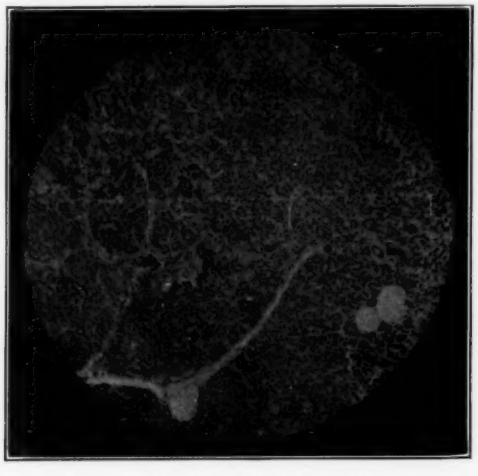

Fig. 13.—(120520). Microphotograph. Chronic pancreatitis. Interacinar fibrosis most marked.

Hypertrophy of the islets was observed grossly and in section from all portions of the gland. Grossly the largest ones appeared as creamy white bodies. Microscopically the close relationship of these hypertrophic islets to the ducts was very noticeable. They varied from slightly above normal to twenty times their normal size, the largest islet measuring 6 mm. in its greatest diameter.

Microscopic Pathology of Hypertrophic Islets.—There is a great variation in the size of the hypertrophic islets; they vary from 0.5 mm. to 6 mm. in diameter.

Most of them are round or oval, on section, although many do not conform to this shape. In a few cases examination of all the sections showed only a few hypertrophic islets in each case; usually they were found in greater numbers. They are found in sections from all portions of the pancreas, but in a few cases all which were observed were in the duodenal portion. Connective tissue in the islets is always increased and the capsule surrounding the islet is always thickened (Fig. 14). Hypertrophic and hyperplastic epithelial cells are found in these islets, and in a few, migration of these hyperplastic epithelial cells takes place; they pass through the three successive stages of neoplasia.

*Primary Cytoplasia.**—The arrangement of the cells in the islets in short single and double cordons and masses between the capillary loops is similar to the normal. Most of the epithelial cells of these islets are differentiated; some are hypertrophic and the outline of the cytoplasm in these is not well defined (Fig. 15). These islets have a thickened connective tissue capsule and a diffuse

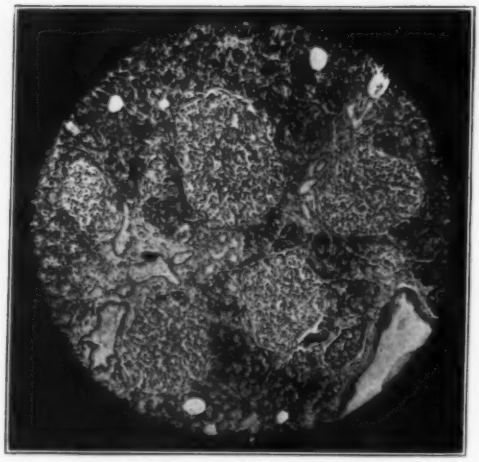

Fig. 14.—(A58947). Microphotograph of hypertrophic islets. Stage of pancreatico-primary-adenocytoplasia.

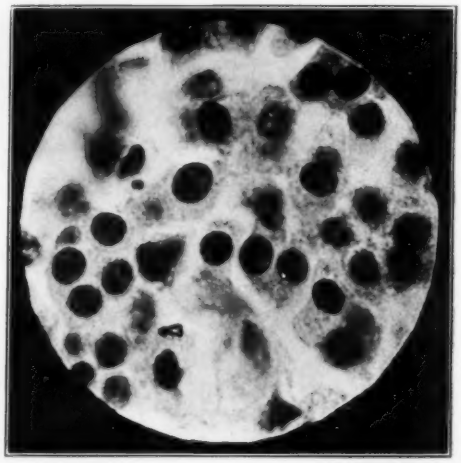

Fig. 15.—(A116521). Oil immersion microphotograph of hypertrophic islet. State of pancreatico-primary-adenocytoplasia.

fibrosis throughout. They are .5 mm. to 1 mm. in diameter. The capillary blood vessels have slightly thickened walls. No leucocytes or lymphocytes are to be seen nor is there any other evidence of an inflammatory process of the islets except a fibrosis.

Secondary Cytoplasia.—The cordons formed by the epithelial cells are more marked than in the normal islet. Most of the cordons are formed by single rows of epithelial cells, a few by double rows. In the sections these cordons follow the contour of the blood vessels and where the vessels are sectioned transversely the cordons encircle them. The epithelial cells are undifferentiated or partially differentiated. Some of the undifferentiated cells are hypertrophic. The number of epithelial cells has increased markedly, but all the cells are confined within the

*MacCarty's terminology of stages of neoplasia:
Primary cytoplasia = Hypertrophy of regenerative cells plus presence of differentiated cells.
Secondary cytoplasia = Hyperplasia of regenerative cells plus absence of differentiated cells, with or without partial differentiation.
Tertiary cytoplasia = Hyperplasia of regenerative cells plus migration, with or without partial differentiation.

connective tissue capsule (Figs. 16, 17 and 18). Some of these hypertrophic islets with hyperplasia of the epithelial cells are very large (0.6 mm. to 1.5 mm.). The capsule is of dense fibrous connective tissue and fibrosis is diffuse throughout the islet. The capillary blood vessels have increased in proportion to the size of the islets and the vessel wall is thickened. There is no evidence of inflammation except fibrosis.

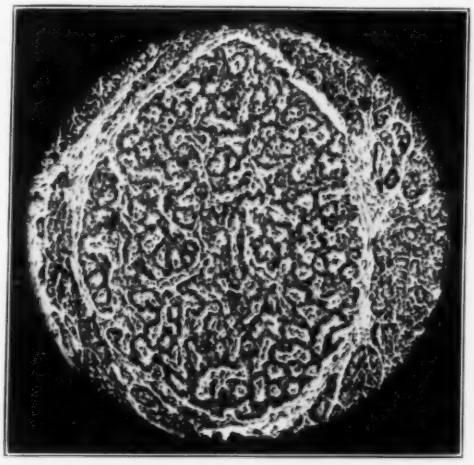

Fig. 16.—(A50276). Microphotograph of hypertrophic islet. Stage of pancreatico-secondary-adenocytoplasia.

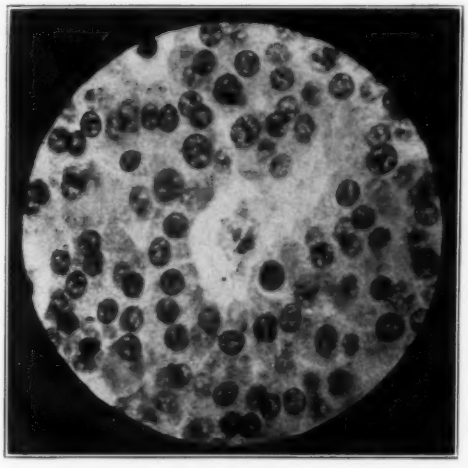

Fig. 17.—(A50276). Oil immersion microphotograph of epithelial cells in hypertrophic islet. Stage of pancreatico-secondary-adenocytoplasia.

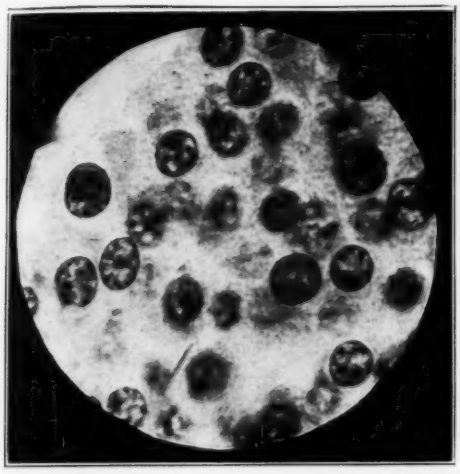

Fig. 18.—(A50276). Oil immersion microphotograph of epithelial cells in hypertrophic islet. Stage of pancreatico-secondary-adenocytoplasia.

Tertiary Cytoplasia.—The cordons are not well defined; most of the cells are in masses. The epithelial cells are undifferentiated; some, however, in some islets show partial differentiation. They are hypertrophic and hyperplastic, there being a marked increase in the size and number. In the center of some of the islets there is an area of cellular debris as the result of cellular disintegration; a few nuclei can be identified in this area. Migration of the epithelial cells

through the connective tissue may be seen at the periphery. This migration of the epithelial cells is evidence of a carcinoma (Figs. 19 to 24). These islets are very large, the largest being 4 mm. by 6 mm. Proliferation of the connective tissue is very marked throughout the islet and the capsule is thick and densely

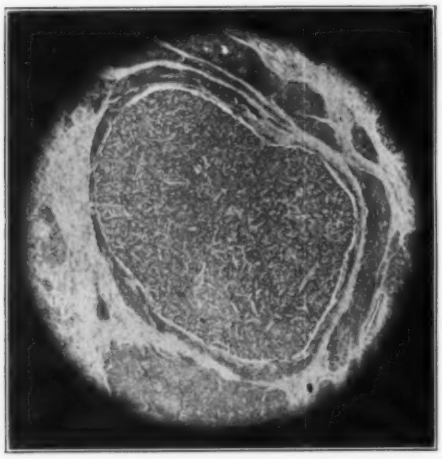

Fig. 19.—(A26398). Microphotograph of islet showing hypertrophic, hyperplastic epithelial cells with migration of these cells through connective tissue capsule. Stage of pancreatico-tertiary-adenocytoplasia.

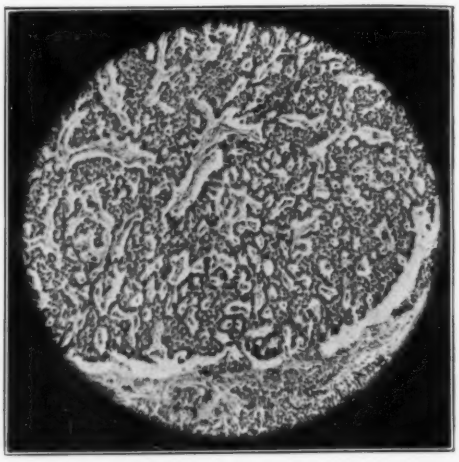

Fig. 20.—(A26398). Microphotograph of periphery of islet showing hypertrophic, hyperplastic epithelial cells with migration of these cells through connective tissue capsule. Stage of pancreatico-tertiary-adenocytoplasia.

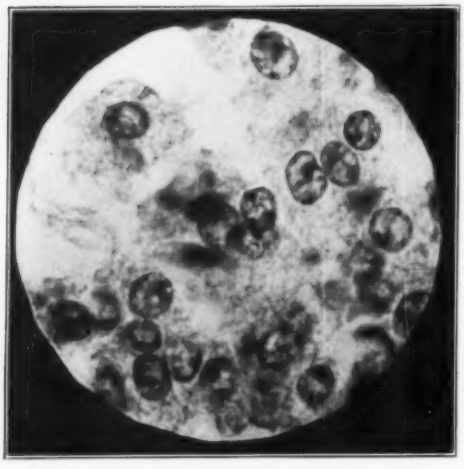

Fig. 21.—(A26398). Oil immersion microphotograph of islet cells showing hypertrophic, hyperplastic epithelial cells. Stage of pancreatico-tertiary-adenocytoplasia.

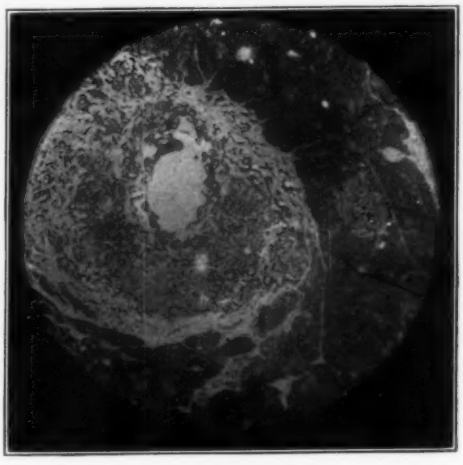

Fig. 22.—(A50276). Microphotograph of islet showing hypertrophic, hyperplastic epithelial cells with migration of these cells through connective tissue capsule. Stage of pancreatico-tertiary-adenocytoplasia.

fibrous. Bands of fibrous tissue pass out from the capsule of the islet into the interacinar and interlobular connective tissue. The blood vessels are very large, but their size is in proportion to the size of the islet, and their walls are thickened.

DISCUSSION

The islet areas in the pancreas were first described by Langerhans, who considered them to be the end apparatus of nerve fibers. From the collective embryologic, cytologic, and histologic studies of later workers, foremost among them Renaut, Laguesse, Opie, Lane, Lewis, Thyng, Dewitt, and Bensley, it has been well established that the islets are, histologically, a definite epithelial unit of the pancreas developed from the epithelium of the primitive anlages, without duct connection, with a rich capillary blood supply, and a hormone-secreting function.

Hypertrophy of the islets, and adenomas of the islets, are the only conditions reported in the literature which could be considered precancerous. Hypertrophy has been reported mostly in connection with diabetes. It is not characteristic of diabetes, however, neither is it to be found in all cases of diabetes. Nichols, Helmholtz, and Cecil have reported cases of a single hypertrophied islet in the

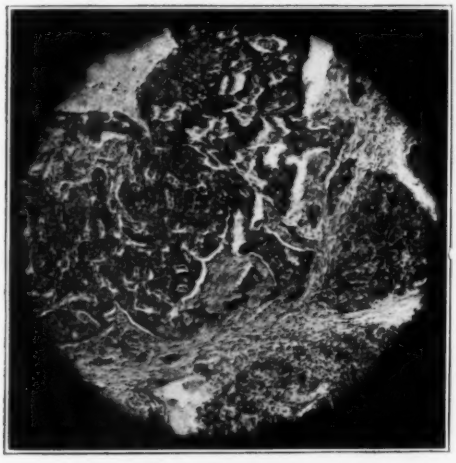

Fig. 23.—(A50276). Microphotograph of periphery of islet showing hypertrophic, hyperplastic epithelial cells with migration of these cells through connective tissue capsule. Stage of pancreatico-tertiary-adenocytoplasia.

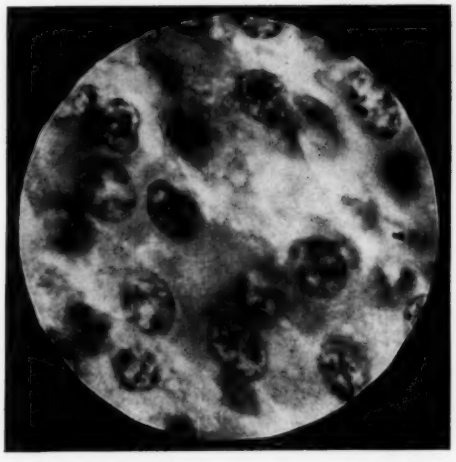

Fig. 24.—(A50276). Microphotograph of islet cells showing hypertrophic, hyperplastic epithelial cells. Stage of pancreatico-tertiary-adenocytoplasia

pancreas. Nichols and Helmholtz each considers his case to be an adenoma while Cecil reports his case an hypertrophy of the islet.

After reviewing the literature I find that most writers classify carcinoma of the pancreas either as alveolar or canalicular.

In 1903, Fabozzi reported his study of the pancreatic tissue taken from 5 patients who had died from carcinoma of the pancreas and tried to establish from these the histogenesis of carcinoma of the pancreas. His deduction is that all carcinomas of the pancreas have their origin in the islets. His illustrations are diagrammatic, and his descriptions are not sufficiently conclusive to be accepted by later writers.

It is not reasonable to assume that all neoplasms in a mixed gland, like the pancreas, originate in one only of its three epithelial units. It is more logical to assume that a neoplasm may originate in any one of the epithelial units, the ducts, the acini, or the islets. From a biopathologic point of view the histogenesis of

neoplasia of the pancreas should be studied in each of these. Under suitable pathologic conditions, each epithelial unit could be expected to produce undifferentiated cells from its germinative tissue; but the study must be made from the tissues which show the changes antecedent to carcinoma. When neoplasia is

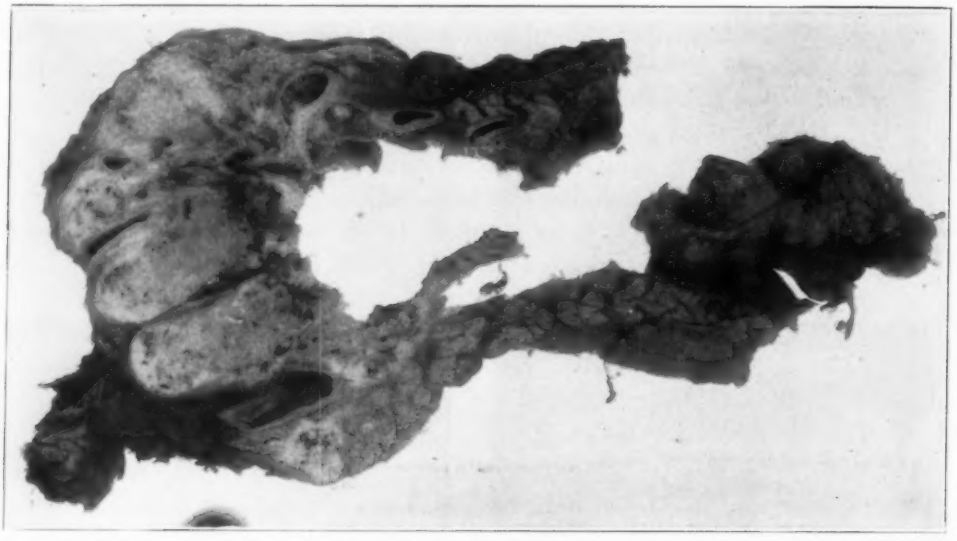

Fig. 25.—(A142013, Aut. 269, 1915). Advanced carcinoma of pancreas.

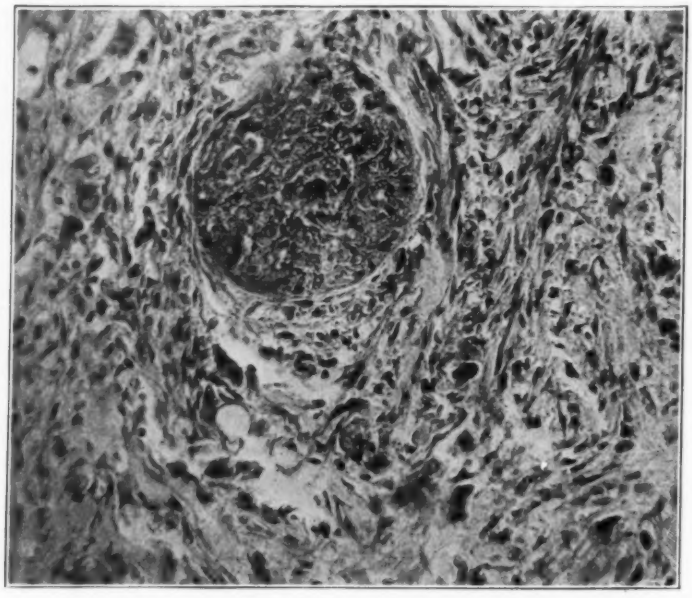

Fig. 26.—(A142013, Aut. 269, 1915). Microphotograph of section from advanced carcinoma of pancreas showing degenerating epithelial cells in dense fibrous tissue and fibrosis of islet.

well advanced or has caused death, it is impossible to establish the site of origin or the successive pathologic changes from the tissue removed at operation or at necropsy; it is because pathologists have tried to prove the histogenesis from tissue

removed at necropsy, after malignancy has caused death, that the histogenesis of carcinoma of the pancreas has not been established (Fig. 25). In a microscopic study of advanced carcinoma of the pancreas we find small masses of cells in the dense fibrous connective tissue. In their form and arrangement they may resemble small ducts, or acini, but if carefully scrutinized they will prove to be groups of degenerating cells. They are epithelial cells, but whether they are degenerating acinic cells or degenerating cells of neoplasia can not be determined (Fig. 26).

The histogenesis of carcinoma of the pancreas must be studied from portions of the pancreas which are too small to be recognized in the gross specimen as carcinoma. For this reason I selected for the study of the early neoplastic changes a series of cases which show chronic inflammation. In the course of the investigation I found a definite hypertrophy and hyperplasia of the islets of Langerhans. This condition was found in about 25 per cent of the cases of

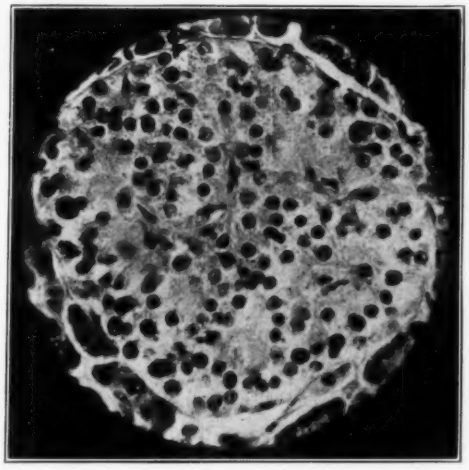

Fig. 27.—(A122622). Microphotograph showing hyalinized fibrosis of islet.

chronic interacinar and interlobular pancreatitis which was associated with chronic gastric and chronic duodenal ulcer. In these hypertrophic islets hypertrophy, hyperplasia, and migration of the cells were observed.

In the hypertrophic islets I found hypertrophic differentiated cells. Accompanying this cellular hypertrophy the connective tissue within and surrounding the islets had increased to protect the adjacent cells from encroachment.

In similar islets I sometimes found also hyperplasia of undifferentiated epithelial cells. These undifferentiated cells, however, are distinctly confined within the dense capsule of the islet.

In some of the hypertrophic islets I found hyperplastic undifferentiated cells migrating through the capsule, a condition which is undoubtedly carcinoma.

These three graphic descriptions apparently represent the stages of neoplasia as described by MacCarty in other epithelial tissues.

Simple fibrosis and sometimes hyalinized fibrosis were the only purely inflammatory reactions found in this series (Fig. 27).

The biologic reactions in the epithelial cells of the islets in the pancreas conform to those that have been observed in epithelial cells in other tissues. MacCarty has pointed out that each organ should be studied from the standpoint of each histologic unit; that each histologic unit must be considered alone from the standpoint of regeneration in all its phases; and that each phase should be named with a descriptive term applicable to that tissue; these biopathologic reactions of the epithelium of the islets in the pancreas might then be described as follows:

$$\text{Pancreatico}\begin{Bmatrix}\text{primary}\\ \text{tertiary}\\ \text{secondary}\end{Bmatrix}\text{adeno-cytoplasia}$$

These descriptive terms are expressive of the successive biopathologic reactions in the regeneration of cells in neoplasia in the islets of the pancreas.

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THE EFFECTS OF HEAVY METAL SALTS UPON A PROTEIN AND THE REVERSAL OF SUCH EFFECTS*

By Robert A. Kehoe, Cincinnati, Ohio

I. INTRODUCTION

IT IS generally held that the toxic effect of the heavy metal salts upon protoplasm is due to the "coagulation" of the proteins, and that this reaction is irreversible. Such a conception necessitates the conclusion that cells and tissues once exposed to the action of the heavy metal salts can not be restored to their normal state, and that death of the affected cells or tissues is inevitable. However, the occasional recovery of a laboratory animal, or an individual, after the administration of an accepted lethal dose of such a toxic salt, suggests that there may be conditions under which the reaction of the heavy metal salts with protein need not be irreversible.

In the treatment of heavy metal poisoning our present methods try, either, (a) to introduce some chemical that will react with the toxic salt and precipitate it in an insoluble or inert form, or, (b) to meet the disastrous effects of such poisoning (as the "acidosis") through the administration of alkalies. It would seem equally wise, if feasible, to attempt to maintain the tissues in their normal physical state in spite of the presence of heavy metal salts, or, if change in physical state has occurred, to try to restore them to normal. The following paragraphs give the results of experiments on protein (gelatin), with this idea in mind. They show that *the coagulation of this material by salts of the heavy metals represents a reversible reaction, in that coagulated mixtures may be brought back into "solution," through treatment with properly chosen lighter metal salts.*

II. EXPERIMENTAL METHODS

By exposing a viscid "solution" of gelatin to low concentrations of various heavy metal salts, we tried to simulate, as nearly as possible, the conditions for heavy metal poisoning as seen in the living organism. The standard gelatin solution used in the following experiments was prepared from a high grade commercial product. Six grams of dry gelatin were added to 300 c.c. distilled water, brought just to a boil, the mixture being stirred until complete solution had been accomplished. When cooled to room temperature, this solution, after several hours, set into a viscid mixture, which, with some difficulty, could be pipetted into test tubes. Preliminary experiments showed the optimal limits of concentration between which satisfactory coagulation of the gelatin could be produced by various heavy metal salt solutions. They also showed that the formation of foam, on mixing the gelatin with the salt solutions, could be avoided and uniform distribution of the two in each other be assured, by adding the salt solutions to the gelatin slowly, while stirring the mixture constantly, by means of the pipette

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containing the salt solution. This method was followed throughout all the experiments.

III. EXPERIMENTS

Fig. 1 illustrates the coagulation of gelatin by silver nitrate. Each tube contains 5 c.c. of 2 per cent gelatin, to which there were added, in the case of Tube 1, 5 c.c. distilled water, and into each of the rest, 5 c.c. M/500 silver nitrate. The photograph shows the coagulated gelatin in those tubes to which the silver salt was added, 48 hours later. At this time there were added to Tubes 1 and 2, 5 c.c. distilled water; to Tube 3, 5 c.c. M/3 sodium sulphate; to Tube 4, 5 c.c. M/3 magnesium sulphate; to Tube 5, 5 c.c. M/10 potassium hydroxide. Fig. 2 shows the results 36 hours later. Tubes 1 and 2, it will be observed, are left

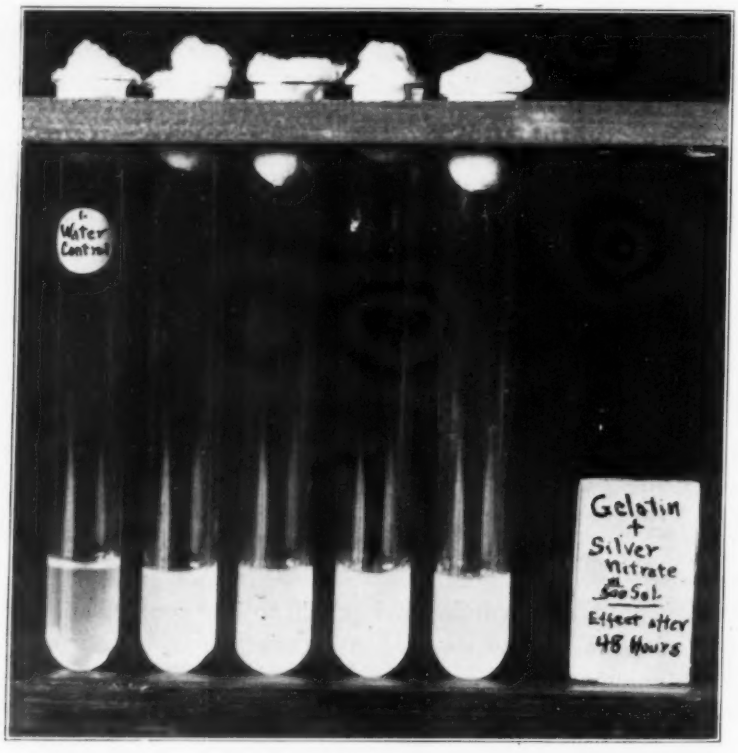

Fig. 1.

unaffected. Compared with the control Tube 2, Tubes 3 and 4 show decidedly less coagulation, while in Tube 5 complete resolution has been obtained.

In Fig. 3 are shown the reversing effects of adding a series of lighter metal salts to a series of gelatins previously coagulated through the addition of 5 c.c. M/500 cupric sulphate, M/1500 ferric sulphate, and M/1000 lead chloride, respectively, to 5 c.c. of 2 per cent gelatin. The reversing agents were added 48 hours after the treatment of the gelatin with the coagulant. The photograph was made 24 hours later. In the cupric sulphate group the concentrations of sodium iodide and potassium hydroxide used were just sufficient to cause a coloring of the

mixture without actual precipitation of the colored copper salts. In the lead chloride group the concentration of potassium hydroxide caused a slight precipitation of lead hydroxide, with the formation of the white ring seen near the

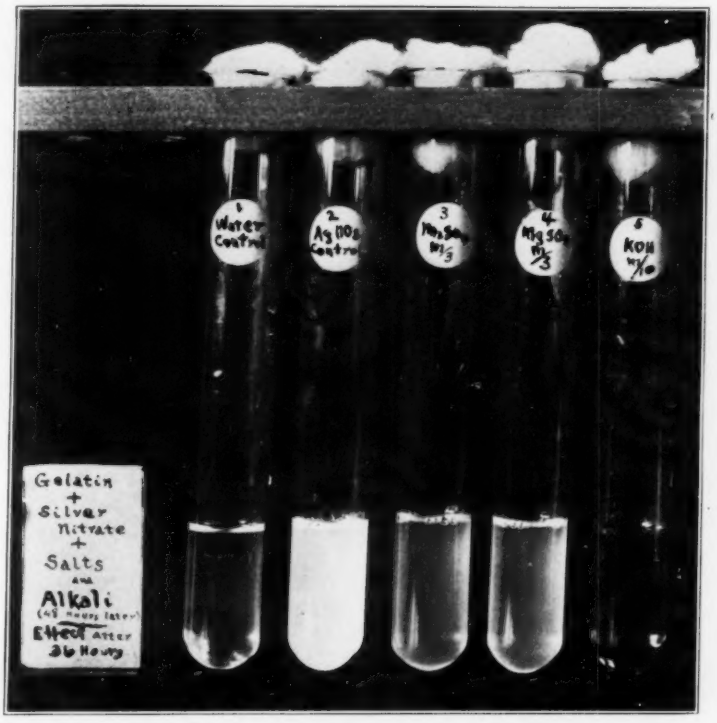

Fig. 2.

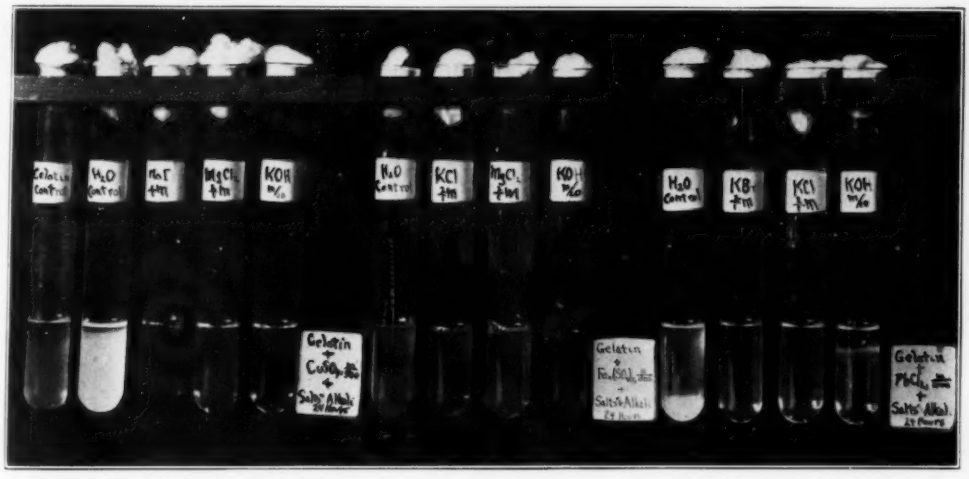

Fig. 3.

upper level of the contents of the tube. In all these tubes the resolution of the original heavy metal coagulum has been obtained, as may be seen by comparison of these tubes with the controls, to which only water was added. In the ferric

sulphate group the results are least distinct, yet, even here, the coagulated material, seen somewhat faintly at the botom of the control tube, is absent in the tubes treated with lighter metal salts and hydroxide.

It is seen from these experiments that coagulation of gelatin by heavy metal salts may be reversed by a number of neutral salts of the lighter metals and by alkali hydroxides. Many salts, other than those indicated in Figs. 1, 2, and 3, accomplish the same results, and in fact it may be said in general that all salts or hydroxides of a lighter metal tend to resolve a heavy metal protein coagulum. Since, however, many of these produce insoluble heavy metal salts, they are not described in this paper, for the reason that the reversal of coagulation, in the

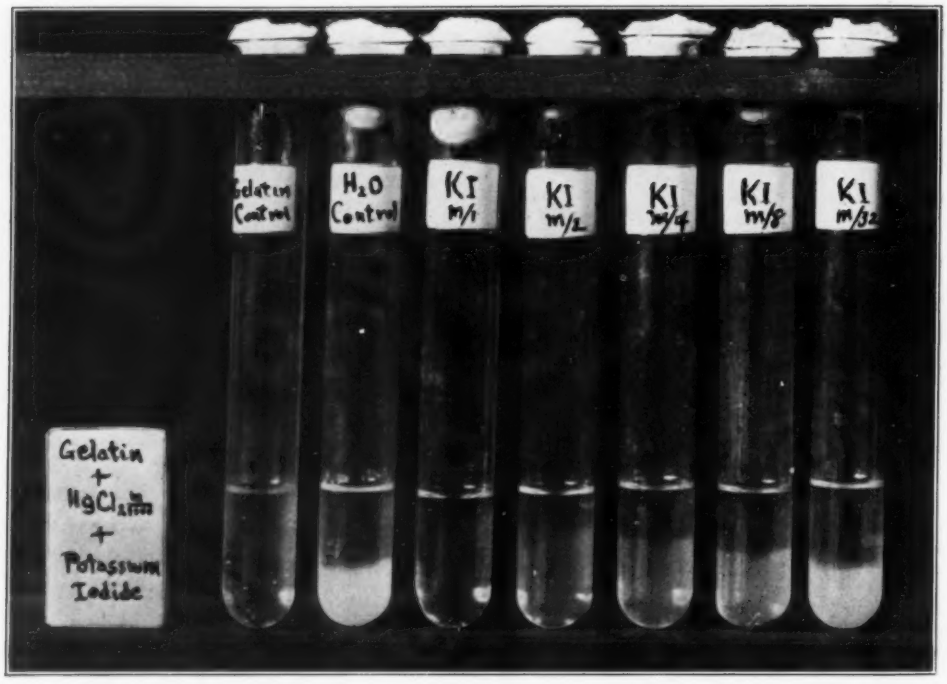

Fig. 4.

experiments described herein, is not a matter of removing the coagulant through its precipitation. No such direct reaction with the heavy metals is apparent in the concentrations at which we worked, except in the cases to which special attention is called.

The importance of the concentration of the salt employed as reversing agent is shown in Fig. 4. To each of the tubes were added, originally, 5 c.c. 2 per cent gelatin, and with the exception of the control, to which only 5 c.c. distilled water were added, each was treated with 5 c.c. M/1000 mercuric chloride. Twenty-four hours later, 5 c.c. distilled water were added to the first two tubes on the left (controls), while to each of the others 5 c.c. of potassium iodide solution of the concentrations M/1, M/2, M/4, M/8, and M/32, respectively. The photograph, taken 24 hours later, shows complete reversal of the mercury coagulation

in the tube to which M/1 potassium iodide was added, less reversal in the next, and so on in decreasing degree to the end of the series.

Fig. 5 shows the results of a similar series of experiments, when 5 c.c. 2 per cent gelatin, treated with 5 c.c. M/1000 mercuric chloride were subjected, 24 hours later, to the action of different concentrations of potassium sulphocyanate. The tube on the left is a control, to which only 5 c.c. distilled water were added, the remaining tubes containing 5 c.c. respectively, 2M, M, M/2, M/4, and M/8 potassium sulphocyanate.

Fig. 6 shows a series of tubes, arranged in the same manner as those in Fig. 5, except that M/200 mercuric chloride was employed as the coagulant.

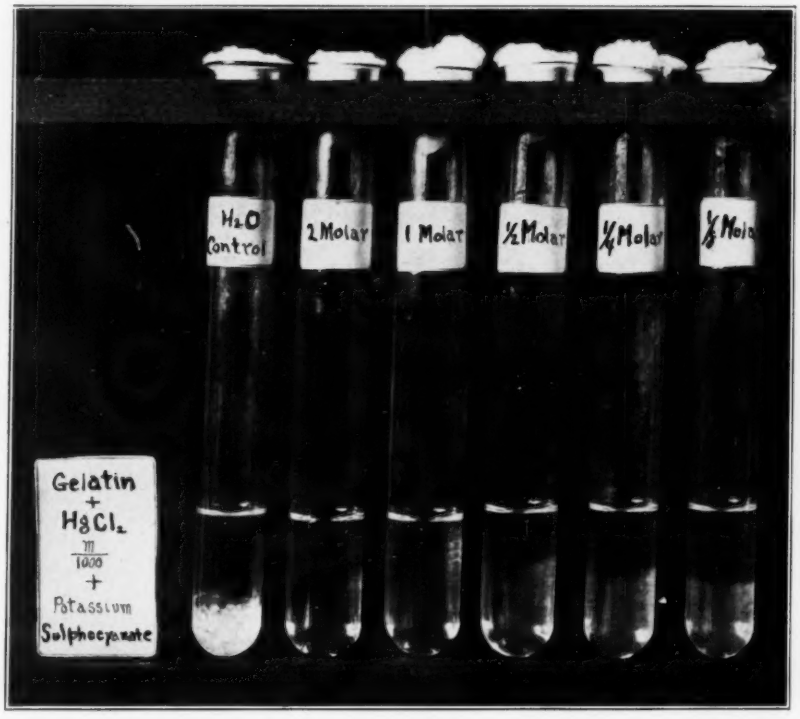

Fig. 5.

While in Fig. 5 both dimolar and molar concentrations of potassium sulphocyanate have brought about complete resolution of the mercury coagulum, in Fig. 6, only dimolar concentration brought about complete resolution. Comparison of corresponding tubes in the two figures shows in every other instance a better degree of reversal in tubes containing the lower concentration of the coagulant.

The speed of the reaction of reversal, and the degree to which it takes place, have been found to depend greatly upon the acid radical of the salt used as the reversing agent. Fig. 7 shows the reversal obtained by a series of potassium salts. Here, to each of a series of tubes containing 5 c.c. 2 per cent gelatin, were added 5 c.c. M/1000 mercuric chloride. To the first were added, 24 hours later, 5 c.c. M/10 potassium hydroxide, and to the others, respectively, from left to right, molar concentrations of potassium sulphocyanate, iodide, bromide, chloride,

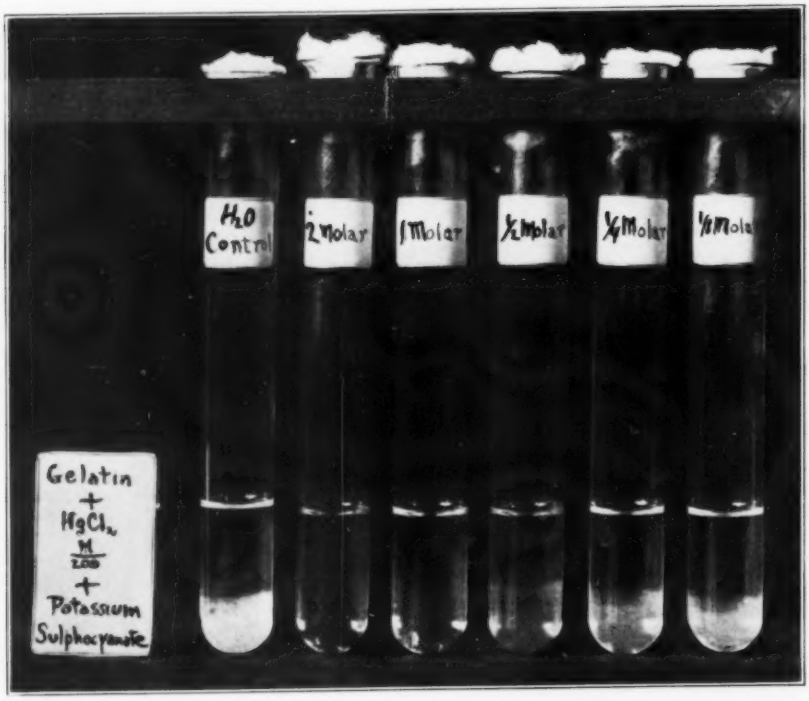
H2O Control
½ Molar
1 Molar
Gelatin
+
HgCl2
M/200
+
Potassium Sulphocyanate

Fig. 6.

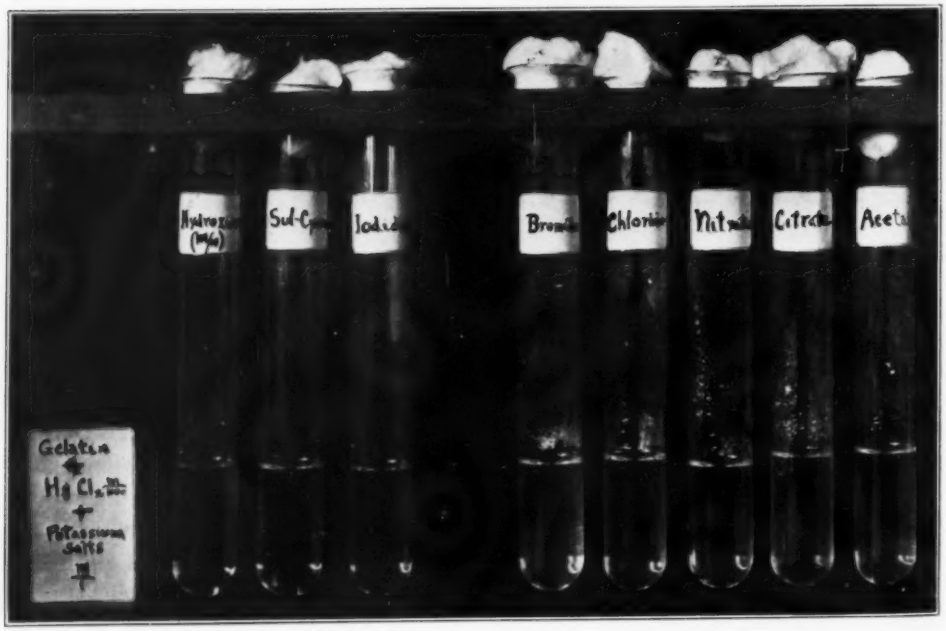
Sul-C
Iodid
Brom
Chlorid
Nitrat
Citrat
Aceta
Gelatin
+
HgCl2
+
Potassium Salts
+

Fig. 7.

nitrate, citrate, and acetate. Resolution was obtained first in the tube to which the hydroxide was added; next in that of the sulphocyanate, and then in that of the iodide. All the others were much slower, neither was complete reversal brought about by any of them in the concentrations employed. Very little difference is observable in the action of the bromide, chloride, nitrate, citrate, and acetate, but they arrange themselves approximately in the order named, the bromide affecting reversal slightly more quickly than the chloride, etc.

The resolution of the coagulated gelatin, under the influence of salts and hydroxides, is hastened by the application of heat to the mixture. Fig. 8 illustrates this fact. To each of 3 tubes, containing 5 c.c. 2 per cent gelatin, 5 c.c.

Fig. 8.

Fig. 9.

M/500 silver nitrate were added. Forty-eight hours later there were added the following: to Tube 1, 5 c.c. distilled water; to Tube 2, 5 c.c. M/3 sodium sulphate; to Tube 3, 5 c.c. M/3 magnesium sulphate. These tubes were immediately put into a boiling water-bath, and left for 15 minutes. Upon removal from the bath all were clear, but on cooling gradually to room temperature, the result was as photographed. Thus the application of heat caused a complete reversal of coagulation in a very short time, while at room temperature such reversal requires from 12 to 72 hours.

We further observed, in the course of the experiments, that the time required for obtaining complete reversal of a heavy metal coagulation, varied greatly with the length of time elapsing between the addition of the coagulant and the addition of the reversing agents, in that the longer this interval of time (up to three days), the longer was the time required for obtaining complete re-

versal. Coagulation of gelatin by heavy metal salts is apparently a slow reaction, requiring in this case several days to go to completion.

The foregoing experiments have dealt with the *resolution* of gelatin coagulated by heavy metal salts. The experiment illustrated in Fig. 9 shows that it is also possible to *prevent* such coagulation. To 5 c.c. 2 per cent gelatin in each of Tubes 1, 2, and 3, were added, respectively, 5 c.c. distilled water, 5 c.c. M/3 sodium sulphate, and 5 c.c. M/3 magnesium sulphate. Immediately, into each of the tubes were introduced 5 c.c. M/500 silver nitrate. The photograph, taken an hour later, shows coagulation in control Tube 1, and complete inhibition of coagulation in Tubes 2 and 3, no coagulation resulting subsequently.

IV. THEORETICAL CONSIDERATIONS

The belief that proteins, coagulated through the action of heavy metal salts, might by appropriate means be brought back to a state more nearly like that of "normal" protoplasm, was suggested by the analogy which exists between the colloid-chemical behavior of the soaps and that of the proteins, in the presence of various alkalies and salts. It has been found possible to convert the poorly hydrated and insoluble heavy metal soaps into highly hydrated and soluble light metal soaps, by treating the former with the hydroxides, carbonates, or neutral salts of the light metals.[1] Therefore, it seemed reasonable to expect that a similar possibility should exist in the case of the proteins (or protoplasm), coagulated by heavy metals, if such coagulated materials could, in truth, be considered to be metal protein compounds comparable to heavy metal soaps. By such means, insoluble and poorly hydrated heavy metal proteinates, analogous to the heavy metal soaps, might be converted into soluble and more highly hydrated lighter metal proteinates, analogous to the lighter metal soaps. Our experiments justify such belief, so that it seems quite probable that the changes suffered by gelatin, and other proteins,* under the influence of heavy metal salts of low concentration, are due to the formation of particles of poorly hydrated and insoluble heavy metal proteinates; that upon treatment of such heavy metal proteinate, with a salt or hydroxide of a light metal, in proper concentration, a replacement of the heavy metal by the light one results, with the formation of a new compound, a light metal proteinate, more highly hydratable and soluble. The speed and completeness of such a double decomposition, as in all such reactions, are dependent upon the concentrations of the reacting materials, and upon the temperature at which the reaction takes place.

V. PRACTICAL APPLICATIONS

Obviously, the practical application of the facts herein observed, regardless of any theoretical explanation of their occurrence, may well be of importance. If the toxicity of the heavy metal salts is due to the coagulation of the proteins of the body, and if we may restore such coagulated proteins to their former state, by the introduction into the body of proper salts and alkalies, we are thus able to combat intelligently the primary toxic effects of the heavy metal salts.

*Incomplete experiments on a protein of the globulin type, casein, indicate that the facts herein observed with regard to gelatin are also true in the case of casein.

The use of neutral salts and alkali carbonates in heavy metal poisoning has been recommended by Fischer,[2] as a means of combating the acid intoxication which is a constant accompaniment of such poisoning. Weiss[3] has reported a number of cases of mercuric chloride poisoning, in which the results of alkaline and salt therapy fully justify their use. MacNider[4] found a marked influence on the part of sodium carbonate, in protecting the kidneys of experimental animals from a degree of damage otherwise the inevitable result of heavy metal poisoning. In these cases, no other end was sought, and no other explanation of results was considered, than that of the neutralization of the effects of a secondary acid intoxication. Doubtless, however, the beneficial effects obtained need not have been due entirely to the overcoming of an "acidosis." They may well, at least in part, have been due to a direct inhibition or reversal of coagulation of the affected body proteins, through replacement of the heavy metal in the coagulated protein by a lighter metal.

I hold that the long-established empiric practice of administering potassium iodide to the victims of chronic lead poisoning,[5] may also be understood in terms of the experiments described above. Any relief of an acid intoxication, by such a neutral salt as potassium iodide, is, of course, out of the question, and the idea that lead is precipitated in insoluble form is negatived by the observation that this heavy metal is eliminated in increased amount, under such therapy. These apparent contradictions are easily explained on the basis of the replacement of the lead, in combination with body proteins, by the lighter potassium. By this means, not only is the coagulated protein brought to a more nearly normal condition, but the combined lead is converted into a diffusible lead salt, easily excreted. Such reversal is accomplished by a concentration of iodide quite insufficient to cause precipitation of lead iodide.

In view of the fact that the presence of sufficiently high concentrations of light metal salts prevents the coagulative action of heavy metal salts upon proteins, the question arises, as to whether the use of potassium iodide, along with mercury and arsenic, in the treatment of syphilis, is a bad or a good therapeutic measure; whether potassium iodide may not inhibit the action of the heavy metal upon the organism of the disease, as well as upon the proteins of the body; or, whether, if used in proper amount, it may not maintain such diffusibility of the heavy metal as to render more easy the attack upon the organism, while at the same time lessening the damage to the tissues of the body.

In the therapy of all heavy metal poisonings, there is a twofold problem, (a) that of combating the primary coagulative effects of the heavy metal upon the body proteins, and (b) that of combating the secondary acid intoxication. The solution of the former problem has been attempted through the precipitation of insoluble salts of the heavy metal. That "insoluble" salts are not without toxic effects, however, is shown by the well-known behavior of such salts as mercurous chloride. It would seem that a better method would be such as would restore the tissues to a more nearly normal state, and, at the same time, release the toxic metal from its combination, converting it into a diffusible salt readily eliminated from the body. Our experiments indicate that such a method is probably feasible, through the use of suitable salts of the light metals. Such salts have the addi-

tional advantage of being the best therapeutic agents for the treatment of the secondary acid intoxication.

To bring about the restoration of coagulated tissues, in heavy metal poisoning, a sufficiently high concentration of suitable salts should be obtained in the body at the earliest possible time. The salts which can be introduced into the body and maintained at relatively high concentrations for long periods of time, without damage in themselves, are the salts of sodium and potassium. The salts, which in terms of our experiments, should be most effective, are the sulphocyanate and the iodide, but, since the effect of high concentrations of these salts upon the body is likely to be severe, other salts will probably prove to be of greater practical value. Especially are the bicarbonates and carbonates to be recommended because of their value in neutralizing acids. Such salts should be used, not in the customary doses of a few grains, but in large doses up to the limit of tolerance, if any results in the way of a reversal of coagulation are to be expected.

V. SUMMARY

(A) The coagulation of such a protein as gelatin, under the influence of heavy metal salts, is not an irreversible reaction, but may be reversed through the action of alkalies, or the neutral salts of the alkali and alkaline-earth metals.

(B) Not all salts of an alkali or alkaline-earth metal are of the same value in bringing about such a reversal, there being a marked secondary dependence upon the acid radical combined with the metal.

(C) Reversal of coagulation occurs most readily if the alkali or salt is added *soon* after the mixture of gelatin with coagulant.

(D) The degree and rate of reversal depend upon the concentration of the coagulant and the reversing agent (and upon the temperature).

(E) Coagulation of gelatin, under the influence of heavy metal salts, may be completely inhibited, by the previous or simultaneous addition to the gelatin, of sufficiently high concentrations of alkalies, or the neutral salts of the alkali and alkaline-earth metals.

(F) It is suggested that metal salts react with gelatin to form definite compounds, as do the same metals with the fatty acids to form the soaps.

(G) Suggestions are made as to the treatment of poisoning brought about by heavy metals.

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THE TUBERCULOSIS COMPLEMENT-FIXATION TEST*

Report of 700 Cases

By B. Stivelman, M.D., Bedford Hills, N. Y.

So many extraordinary claims have been made for the tuberculosis complement-fixation test in recent years that the impression is conveyed that the burden of diagnosis has been shifted from the clinician to the laboratory worker. It has also been stated that clinical activity, as well as the immediate prognosis, can be determined by means of this test with unprecendented accuracy. To test the validity of these assertions, we performed the tuberculosis complement-fixation test in 700 consecutive cases admitted to our sanatorium. We endeavored to ascertain

1. The diagnostic value of the test.
2. What light does this test shed on the activity of the process when a diagnosis has been made?
3. The relative value of the test in the different stages of the disease.
4. The prognostic value of the test.

We used exclusively Miller's bacillary suspension and a similar antigen prepared by the Board of Health of New York City. The efficiency of both antigens was found to be identical. A Wassermann test was done on all the cases without exception. All patients were examined roentgenologically and at least by three clinicians independently. The average stay of all patients was over six months. In no instance did the laboratory worker obtain information about patients whose blood was examined.

Diagnostic value of the test

Positive fixations were obtained in 26, i.e., 24 per cent of 108 nontuberculous individuals. It is noteworthy that two of the three cases of pulmonary abscess and two of the six cases of bronchiectasis gave a positive reaction, thus rendering the correct diagnosis more difficult. The cases of chronic bronchitis and emphysema and those suffering from cardiac diseases gave a very high percentage of positive reactions, but it must be emphasized that all nontuberculous cases were observed for many months and were subjected to repeated and painstaking roentgenologic and physical examinations.

Of 592 sera from definitely tuberculous individuals, 310, or 52.4 per cent gave a positive reaction, and 282, or 47.6 per cent, gave a negative reaction. Over 90 per cent of all the patients with negative reaction were sthenic cases, and the low percentage of positive reactions could not therefore be ascribed to the exhaustion of the process of antibody formation. Of these 282 patients, 176 had a positive sputum.

To eliminate as much as possible the personal factor in estimating activity, we have adopted definite rules as follows: When in a tuberculous patient the pulse rate rose persistently above 90 in the male and 95 in the female, and was due

*From the Montefiore Home Country Sanatorium, Bedford Hills, N. Y.

TABLE I

NONTUBERCULOUS CASES

	POSITIVE FIXATION	NEGATIVE FIXATION	TOTAL
Abscess Pulmonum	2	1	3
Bronchiectasis	2	4	6
Asthma	1	3	4
Chronic Bronchitis and Emphysema	4	17	21
Cardiacs	4	6	10
Hyperthyroidism	2	2	4
Hysteria		1	1
Syphilis	1	4	5
Malignancy (Gastric)	1		1
Malingering	1	1	2
No definite disease	8	43	51
	26	82	108

to no other ascribable cause, it was judged sufficient to indicate activity. Rectal temperature, rising over 99.8° in the afternoon, was considered to be due to an active tuberculous process. Loss of weight, night sweats, and malaise, even in the absence of fever, signified an active process. Tubercle bacilli in the sputum plus any other constitutional symptoms spelled activity. Patients who coughed and whose sputum was positive for many years, were considered inactive, provided their general condition was good. On the other hand, tuberculous complications in the respiratory, digestive or urinary tracts and frequent hemoptyses, not slightly colored sputum, however mild, were considered as signifying an active process. Dullness on percussion, rales, and abnormal breathing did not influence us to any extent. It is realized that not all observers will subscribe to this description of activity, but our classification is based on these assumptions.

RELATION OF THE TEST TO ACTIVITY OF THE LESION

Of 294 active cases, a positive reaction was obtained in 178, or 60.5 per cent, while of the 298 inactive cases, 132, or 44.3 per cent, reacted positively. (See Table II).

TABLE II

ACTIVITY	NO. OF SERA	FIXATION	SPUTUM
+	294	Pos. 178 or 60.5%	+ 163
			− 15
		Neg. 166 or 55.7%	+ 101
			− 15
−	298	Pos. 132 or 44.3%	+ 80
			− 52
		Neg. 166 or 55.7%	+ 75
			− 91

RELATION OF THE TEST TO THE STAGE OF DISEASE

The classification of the National Tuberculosis Association was strictly adhered to. Positive reaction was obtained in 49, or 33 per cent of 147 incipient cases; 131, or 52 per cent of 248 moderately advanced cases; 130, or 66 per cent of 197 far advanced cases.

TABLE III

STAGE	ACTIVITY	TOTAL	POS. FIX.	%	NEG. FIX.	%
Incipient	+	21	8	38.1	13	61.9
147	-	126	41	32.5	85	67.5
Mod. Advanced	+	132	67	50.8	65	49.2
248	-	116	64	55.2	52	44.8
Far Advanced	+	141	103	73.0	38	27.0
197	-	56	27	48.2	29	51.8

RELATION OF REACTION TO THE IMMEDIATE PROGNOSIS

Of 258 cases whose tuberculosis fixation was positive on admission, 195, or 75 per cent left the institution in various degress of betterment; while of the 270 cases whose fixation test was negative on admission, 85 per cent left similarly improved. It must be noted, however, that the smaller percentage of recorded improvements in the first group was due to the fact that this group numbered most advanced cases who also gave a positive reaction most frequently.

RELATION OF THE REACTION TO HEMOPTYSIS

Of 108 cases who had pulmonary hemorrhages subsequent to admission, 43 had a negative fixation and 65 a positive fixation. Little importance can be attached to this occurrence since hemoptysis occurs more often in the advanced tuberculous who also give a positive fixation more frequently.

RELATION OF THE TEST TO THE WASSERMANN REACTION

Among the 700 sera tested, 11 reacted strongly positive to the Wassermann test, or an incidence of syphilis of 1.6 per cent. Four of these cases had a positive sputum and a negative tuberculosis fixation test and clinical evidence pointed to the coexistence of both diseases. Four were nontuberculous and gave a negative tuberculosis fixation. One was nontuberculous but reacted positively to the tuberculosis deviation test. The two remaining cases we are satisfied suffered from tuberculosis and syphilis, although this was not bacteriologically proved.

OBSERVATION

1. In attempting this study we endeavored to ascertain the diagnostic and prognostic value of the tuberculosis fixation reaction as well as its relation to active and clinically inactive tuberculosis.

2. Since 24 per cent of nontuberculous individuals and only 52.4 per cent of the definitely tuberculous give a positive reaction, it would seem hazardous to permit the test in its present stage of development to influence our clinical judgment.

3. The test did not help us in the differential diagnosis of pulmonary diseases.

4. In pulmonary tuberculosis clinical activity could not be diagnosticated from the results of the complement-fixation test.

5. The test sheds no light on the immediate prognosis.

6. We have no reason to believe that a tendency to cross fixation with a Wassermann reaction really exists.

7. The percentage of positive reactions increased as the disease advanced.

The percentage of positive reactions in definitely incipient tuberculous in our series was only 33 per cent. Thus it is seen that where the test could be of greatest assistance it is least applicable.

I wish to express my indebtedness to Dr. S. Wachsmann, Medical Director of the Montefiore Home, New York City, through whose efforts the work was made possible.

LABORATORY METHODS

TRAUMATIC HEMOLYSIS AND THE SYRINGE METHOD OF BLOOD COLLECTION*

By C. E. Roderick, M.D., Battle Creek, Mich.

IN a recent article Olson† condemns the syringe method of blood collection for complement-fixation test because of the large percentage of serums showing hemolysis.

During the past 27 months, we have used the syringe method of blood collection in 14,500 instances and the number of serums showing hemolysis is not more than 2 per cent. I therefore feel that it would not be out of place to state our method of procedure which is as follows:

A 20 c.c. syringe is sterilized in boiling distilled water or by means of a chemical together with a twenty-two gauge needle. The needle is attached to the syringe and the barrel filled with sterile physiologic salt solution made of chemically pure sodium chloride and freshly distilled water, which is then expelled through the needle. The plunger is then worked up and down in order to expel all the saline possible. A very small amount of the salt solution is permitted to remain for the purpose of lubrication, as a glass syringe is more efficient when moist.

The arm of the patient having been cleansed at the bend of the elbow with iodine or alcohol and permitted to dry, and a tourniquet having been properly applied, the needle is introduced, beveled side up, into the vein and about 20 c.c. of blood withdrawn. Half of this quantity is placed in a chemically clean bottle containing a small amount of sodium oxalate to prevent clotting. This portion is used for chemical analysis. The remaining 10 c.c. are placed in a chemically clean, 15 c.c. dry centrifuge tube. The danger of hemolysis from the force of the plunger of the syringe is overcome by first removing the needle and using only sufficient force to empty the syringe *and no more*. Foaming of the blood is to be avoided, but in a number of instances we find the top of the blood column to have a small amount of foam and in very few cases laking could be attributed to this cause.

The blood is sent to the laboratory as soon as possible after collection; more than an hour is seldom required. The serum is separated in most cases by the use of the centrifuge and placed in the ice chest until the time for the test.

A record of the condition of the serum is kept; in less than 2 per cent do we have laking. I have never seen laked blood give a false positive reaction; the

*From the Battle Creek Sanitarium, Battle Creek, Mich.

†Olson, George Manghill, M.D., Minneapolis, Minn., Traumatic Hemolysis and the Wassermann Reaction, The Journal of Laboratory & Clinical Medicine, January 1920, Page 259.

tendency is rather to be anticomplementary. While this latter result is far from satisfactory to both the patient and the doctor, it is not so fraught with danger as is a false positive reaction.

A more common cause of laked blood than the syringe method itself depends upon the preparation of the syringe. The collector will sometimes sterilize the syringe by the use of chemicals and then rinse the syringe in distilled water instead of salt solution, or will boil the syringe and neither dry it nor rinse it in saline. While it is preferable, it is not absolutely essential to have the syringe sterile. It is far more important to have it free from chemicals and dry; or if moist, with salt solution.

CONCLUSIONS

1. The syringe method, having proved satisfactory, is to be recommended.
2. A proper preparation of the syringe and saline solution will overcome the tendency to hemolysis.

A NEW METHOD FOR THE PREPARATION OF CELLOIDIN SACS*

By C. F. Ulrich, M.D., Cleveland, Ohio.

ANY ONE to whose lot has fallen the preparation of celloidin sacs will undoubtedly appreciate a method which makes for ease and simplicity in preparation and insures a nonleaking finished product.

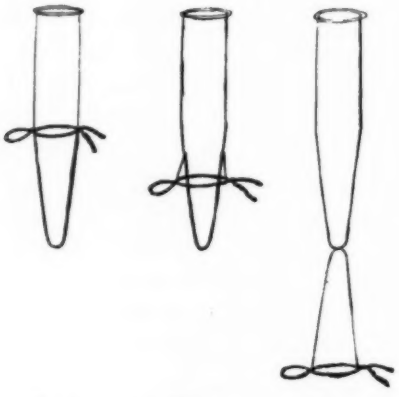

Fig. 1. Fig. 2. Fig. 3.

A 20 c.c. conical centrifuge tube, free from scratches or other imperfections in the glass, is thoroughly cleaned and dried. Strong twine is then tied about the base of the conical portion of the tube (Fig. 1). The tube is immersed in celloidin solution, so that the twine is just covered; is quickly removed and

*From the Cardio-Respiratory Laboratory of the Lakeside Hospital, Cleveland, Ohio.

rotated until the odor of ether is no longer perceptible. It is then plunged into cold water.

The upper end of the sac is carefully loosened, and the sac is removed by grasping the twine, drawing it down toward the tip of the tube, and inverting the sac (Figs. 2 and 3).

A NEW QUALITATIVE ALBUMIN TEST

By Hal Bieler, M.D., Twin Falls, Idaho

THERE is a rather interesting test, concerning the type of albumin in the urine of certain cases, showing profound toxemia. Several other laboratory workers, including Dr. R. S. Morris, have noted the reaction, and although the prognostic significance has been realized, the actual chemical nature is none too clear.

The reaction is a color change, affecting any copper hydroxide solution, such as Haines or Fehlings solution. The usual technic of the qualitative sugar test is carried out, the copper solution being diluted to a light blue color and heated almost to the boiling point. Upon addition of one drop of filtered urine, a deep purple color is noticed. It is an interesting fact that blood serum gives the same reaction.

Urines giving this reaction have been from cases of great general intoxication, and great renal protein digestion. Ten cases have been seen by the writer. Five were cerebral hemorrhage cases in coma, three were uremia cases apparently approaching coma, and two eclampsia cases. All but one (eclampsia) case died, and in this one case, convulsions had not as yet occurred, and by a quick Cæsarean section and forced elimination this patient, by a miracle, recovered.

This test increases then, the gravity of the prognosis, almost enough to signify impending dissolution, and should have a laboratory value.

It was noted above that blood serum gives the same reaction. So do also other protein substances when breaking down in the direction of albumoses and peptones—proteins giving the pink Biuret reaction. It is interesting to question whether this protein in the urine is from actual destruction of kidney substance or whether the blood serum is "filtering through." Both are possible.

For helpful explanatory points concerning this reaction, I am indebted to Drs. A. P. Mathews and Martin H. Fischer, of Cincinnati.

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EDITORIALS

The International Health Board

THERE is no health agency in the world doing better or more effective work than the International Health Board. The purpose of this Board is to demonstrate in different parts of the world the efficiency and value of scientific sanitation and to induce, by practical demonstration, the locality to undertake and continue the work. A brief review of the operations of this Board will, we are sure, be of interest to the medical profession. The work was begun in 1910 and directed to the eradication of hookworm disease in certain southern states. While progress in sanitation during the first six years was extremely slow, for the past four years improvement has been continuous and has steadily gained in momentum. Since 1915 the progress in state and local support has been steady. In 1915 the board was compelled to furnish more than eighty per cent of the money necessary to carry on this work. In 1919 the state boards of health and the counties, seeing the great value of the procedure furnished nearly eighty per cent of the money to continue the work. This indicates that the time will come when state and local authorities, having so valuable a demonstration before them, will proceed without help. In the West Indies the hookworm campaign has ex-

tended over British Guiana, Dutch Guiana, Grenada, and many of the West Indian Islands. In Central America it has included Panama, Costa Rica, Nicaragua, Salvador, and Guatemala. The work in Brazil has met with most encouraging results. During the current year (1920) the board will expend $200,000 on the work in Brazil, while the federal and state governments have provided $1,150,000. At first the work of the board was limited largely to the control of hookworm disease, but at present malaria is included in the program. It is intended to cover the whole of the great country of Brazil. State departments of health are being established; existing departments are being more effectively organized, and funds are being liberally provided. The work in the federal district is being used as a training center for representatives from the several states and sentiment is being formed for adequate schools to train workers for positions in the public health service. The government of Colombia contributed $6,000 and Ecuador has asked that the work be extended in that country.

In Ceylon, the Planters Association has given hearty cooperation since the work began in 1916. All areas are sanitated in advance of treatment; sanitation has not been effectively maintained but is steadily improving; government and planters are now supplying half the funds for the demonstrations and are maintaining the sanitary organization and follow-up treatment of the infected.

In the Seychelles Islands, the work has been in progress for more than two years. Infection found in the colony was medium; sanitation was practically zero; work was undertaken with the hope of bringing the infection under complete control. The government has given enthusiastic support from the beginning. The infected area has been covered and resurveys are in progress; advance in sanitation has been slow but steady; new sanitary regulations have been promulgated, and the government has undertaken to organize and maintain permanent central supervision.

In 1917 the board provided funds and carried out a survey in Papua for the government of Australia. For a similar demonstration in Queensland, which followed in 1918, the government provided half the funds. In 1918 the board entered into an arrangement for a program in rural sanitation extending over a period of five years and involving the cooperation of the federal and state governments.

The work in Siam was begun in 1917. For 1920 the government has provided an appropriation of $17,000. If the work is to become self-sustaining it must be not only supported by Siamese funds, but it must be directed by trained Siamese physicians. This means that a medical school in which preventive measures are taught should be established in that country. There is now a government school at Bangkok, but it lacks teachers, equipment, and properly prepared students.

The hookworm work in the Fiji Islands had to be discontinued on account of the necessity of withdrawing the personnel during the war. It is expected that this work will be resumed in the near future. In 1916 the government of Borneo invited the board to cooperate with it in its measures for the control of hookworm disease in that country. This work has been delayed on account of the World War but will be reopened during the present year.

The antimalarial work in different sections of the southern states is being

carried on with marked success. Work during the year 1918 in Sunflower County, Miss., covering a selected area of about 100 square miles, with a population of about 9,000, indicated that within a limited area and under average plantation conditions in the Mississippi Delta, malaria may be brought within reasonable control by destroying the parasite in the blood of the hookworm carrier and this at a per capita cost of about $1.08. In this experiment the board furnished the quinine necessary to sterilize the people. In 1919 an attempt was made to extend this work to a population of about 55,000. The people were required to pay for their quinine, and there was no house to house visitation. Frequent experience showed unsatisfactory results. In Hinds County, Miss., an experiment was undertaken in 1918 to test the applicability of antimosquito measures to rural conditions. The results have been encouraging and the work will be continued during 1920. For four years the board has conducted a series of experiments in towns in Arkansas.

The attempt to control malaria by screening alone was made in a small village in Arkansas. The results showed that about 70.6 per cent of the people were kept free from infection at an annual per capita cost, less overhead, of $1.75. The unit of operation was small; the test was conducted for only one year; unfavorable conditions made it necessary to discontinue it for the time being. To arrive at any fair conclusion, it will be necessary to make the tests more extensive, to carry them out under a variety of conditions, and to extend the test under a given set of conditions over a period of at least three years.

A new experiment in dealing with malaria in the South is being tried. This method was devised and used by Dr. Le Prince of the U. S. Public Health Service in Panama. The experiment is relatively simple; involves whitewashing the dwellings (plantation negro cabins) on the inside, drawing a dark line at a convenient height and enlisting the family (preferably the children) in killing the mosquitoes as they collect on the dark band.

Still another method of dealing with malaria in the Delta of the Mississippi is to be tried during the present year. It is generally believed by public health officers that the cost of malaria control by antimosquito measures on plantations in the Mississippi Delta will be prohibitive. The region is low, level, intersected with a patch-work of swamps and bayous; breeding of Anopheles abundant; tenant houses scattered, located mainly along the banks of bayous. The cost of destroying or controlling breeding places for individual houses is prohibitive. By concentrating the houses on a given plantation at a few points selected with reference to control of breeding places would make it possible to control the breeding for a group of houses at a relatively small cost. The feasibility of this plan, so far as concerns the control of malaria, has been demonstrated on the rubber estates in Malaya, by concentrating coolies in lines and clearing the jungle for a given distance around the lines. It is proposed to make a more careful study of conditions in the Delta, to confer with planters as to the feasibility of the project, and if conditions invite, to carry out the experiment on a selected plantation.

Malaria, like hookworm disease, while distributed over a large part of the globe, is in its more serious forms essentially a tropical and semitropical disease. It is a serious menace to life, health, and working efficiency in most of the coun-

tries in which the board is engaged in the control of hookworm disease. From many countries requests have been received by the board to extend this work for malaria control to tropical regions. The menace of the infection in many of the countries makes these requests peculiarly appealing. However, the control of malaria under tropical conditions is more difficult than it is in our temperate climate. It is, therefore deemed advisable that before undertaking to conduct any demonstration under tropical conditions efforts be made to adapt working methods to those conditions.

Extermination of yellow fever now seems possible. Until recently, Guayaquil in Ecuador has been the hotbed of yellow fever on the Pacific Coast. General Gorgas has been placed in charge of the sanitation of this city. In December, 1918, there were eighty-six cases of yellow fever in Guayaquil. Since July, 1919, there has not been a case. The study of conditions in Guayaquil has not only led to the eradication of the disease from that city, but has given Noguchi opportunity to solve the riddle of the causation of this disease.

In 1918 an epidemic of yellow fever appeared in Guatemala. This was soon traced down and the disease exterminated. Since that time yellow fever has appeared at Merida, Yucatan, and at various points in Salvador, Nicaragua, and Honduras. It is also known to have recently appeared in Brazil. The Brazilian authorities are apparently undertaking energetic measures for its control and it is believed that these will be successful. Very recently yellow fever has been reported on the west coast of Africa, though there is some doubt about the correct diagnosis of the disease. The board will probably send an expert to that region to investigate and to inaugurate such steps as may be necessary to eradicate the disease.

The board is continuing its antituberculosis work in France. This has resulted in a rapid multiplication of tuberculosis dispensaries. Each dispensary provides the services of one or more physicians. French physicians are aiding in this work and it promises to strengthen the bond of union between the two republics.

The above is a brief and imperfect statement of the work that has been done and is being done under the supervision and direction of the International Health Board. It is far-reaching in its influence. To close a statement of the work of the International Health Board without reference to the splendid school for the training of public health officers established by the board in connection with Johns Hopkins University would not be warranted. This school, under the guidance and direction of that great man in both curative and preventive medicine, Dr. Wm. H. Welch, promises great things for the future of preventive medicine in this country. The annual expenditure of the board amounts to more than $2,000,000, and every dollar is spent in the most efficient and economical way. Some centuries ago, a wise Frenchman said that if the human race is to be brought to physical perfection it must be through the agency of preventive medicine. It is pleasant to recognize Mr. Rockefeller as a follower of that great Frenchman, Descartes. Mr. Rockefeller has shown by the expenditure of his millions his great faith in scientific research and in medicine, both curative and preventive.

—*V. C. V.*

The Prohibition Experiment

OUR GOVERNMENT is now making the biggest physiologic and psychologic experiment ever made in the history of the world. Instead of employing rabbits and guinea pigs, we are making this experiment on about 110,000,000 human beings. The medical profession must not permit this great experiment, with all its side issues, to escape observation. In different localities different manifestations of the effect of the experiment will be in evidence. No one thinks, at least it is hardly supposable that any one thinks, that everybody will immediately abstain altogether from alcoholic stimulants. In the large number of cases of poisoning by wood alcohol, and possibly in some instances by amylic alcohol, we have a manifestation of the recklessness with which some people follow their tastes even if the taste be a depraved and abnormal one. However, such instances as these should not give us much trouble. The man who will drink wood alcohol is either so ignorant or so thoroughly abnormal on account of his depraved taste that his life can't be worth a great deal to the state. We shall, therefore, not shed any tears over these losses, except in such instances where they fall upon innocent or ignorant companions. The psychology shown in this experiment is well worthy of study.

Up to the present time our observations have been confined largely to those who were most earnest in securing prohibition. It seems that, to the majority at least of those of this class, their success came rather unexpectedly. They had not dreamed that prohibition would be brought about so suddenly, and that the lid would be clamped down so tightly. Among our acquaintances many most estimable men and women belonging to this class, as soon as they saw that prohibition was likely to be a fact, rushed to centers of supply and bought, many of them at fabulous prices, small or large quantities of alcoholic drink. It seems that they had never really convinced themselves that under all conditions they could do without stimulation. They did not know how soon they would have influenza or something else for which whiskey is reputed to be beneficial. It might be asked whether man has ever known or suffered from any ill in which belief in the beneficial action of alcohol has not been expressed, by some one at least. Years ago when alcohol was plentiful and when teetotalers were not so numerous, even the most devout prohibitionists believed that whiskey was a good thing for snake bites, stings of poisonous insects, for rheumatism, for bad colds, for malaria, in fact for most of the ills that human flesh is heir to. It is difficult for us to shake off these old beliefs and their continued influence upon us led the best of us to try to lay in a little stock before the possibility of getting alcoholic drinks was closed off entirely. We need not be afraid that our prohibition friends who have been laying in their supplies are going to be converted into drunkards. Nothing of this kind will happen. There is apparently innate in man a desire to possess that, the possession of which is difficult. We dare say that a close search in the cellars and cupboards of many of our prohibition friends, both male and female, would disclose the hiding places of bottles containing various kinds of liquid refreshment. These people have stored away these bottles, not with the intention of drinking their contents, but simply

that they might have something which the ordinary individual does not possess or, at least, has difficulty in securing.

We are sorry to see that the distribution of whiskey is to be placed at the discretion of the medical profession. According to the latest reports, any doctor may under certain forms prescribe whiskey, not more than eight or ten ounces every ten days, for any individual. Now the reputable physician is not going to have anything to do with this matter. It will fall, we predict, largely into the hands of the disreputable practitioner, and that it will be abused there can scarcely be any doubt. We are prohibitionists, but we do not believe that the 110,000,000, more or less, of our people are going suddenly to discontinue altogether the use of alcoholic beverages. If the movement now in force can be carried far enough to do away with the saloon and the excessive drinking which has characterized many classes, it will be a blessing. We are sure that the better class of physicians need no caution as to their prescription of alcohol. So far as we know, the medical profession as a whole, has already repeatedly and plainly stated that alcohol in no form is an essential in the treatment of any disease. Notwithstanding this fact, within the last few months, the public as a whole, has apparently acquiesced in the decision of the government that whiskey shall be used, even quite largely, for medicinal purposes. If physicians find that alcohol is essential or is even beneficial in the treatment of any disease, they should record the observations upon which their judgment is formed and should lay their conclusions before the profession. As we stated in the beginning, it is a physiologic and psychologic experiment on a great scale, and the reactions resulting from this experiment should be observed, recorded, and studied most thoroughly.

—V. C. V.

The Toxin-Antitoxin Mixture in Immunization Against Diphtheria

IN the February number of this JOURNAL there appears an editorial expressing caution concerning the administration of this mixture. It was not intended in the editorial to combat or to deny the value of this mixture if properly prepared. Dr. Wm. H. Park, of the Board of Health of the City of New York, has had more experience with this preparation than any one else in the United States. We are glad, therefore, to have his consent to reproduce herewith a letter which he has written to the editor-in-chief. It is as follows:

"I have just read the editorial in your journal. I appreciate the reasons that caused you to write it, but I think that you put too much emphasis upon the dangers. A series of tests just finished in New York yield, I think, the proof that immunity of long duration is offered.

"We have made many studies upon the toxicity of the preparation and find without exception that if the product is properly standardized, it never becomes poisonous; in fact, from month to month it becomes more overneutralized, as the toxin portion of the mixture is less resistant than the antitoxin.

"We have given over 40,000 injections and have never had an accident.

Some 6,000 of these injections were given infants under ten years of age, the amount injected being the same as in older children and adults. Occasionally in older children disagreeable protein reactions occur which give rise to local and constitutional disturbances for several days. We have found that fully ninety per cent become immune after three injections and in those tested after four years this immunity has been found to continue.

"We are so hopeful from these results that we are planning next month to use the Schick test in the pupils of one hundred schools and to urge toxin-antitoxin injections on those giving a positive reaction.

"It is true that in this product we are dealing with a mixture which if improperly prepared might have free diphtheria toxin. If, however, the same precautions are used as with other poisonous drugs there is no reason whatever why any product sent out from a properly officered laboratory should not be entirely safe. Without some form of active immunization it seems impossible to greatly lessen the amount of diphtheria now persisting."

Wm. H. Park,
Bureau of Laboratories, Department of Health,
New York City.

Drainage

A RECENT paper by Horsley[1] on surgical drainage and its biology, calls up a train of thought that leads far beyond the confines set by that author. Horsley calls attention to the fact that the stomach, the rectum, the bladder, and the larynx are able to rid themselves of foreign bodies because they possess a specialized method of protection which depends upon the presence of an anatomic outlet,—by vomiting, by defecation, by urination, and by coughing. These are special examples of the possibilities of drainage which are independent of whatever goes on in the walls of the viscera. In the closed anatomic cavities of the body, as for instance in the peritoneal cavity or in the pleura, attempts may indeed be made to evacuate a foreign substance but such efforts will be not appreciated except as they are indicated by histologic changes which occur in the walls of the cavities. In these walls, as in those of the hollow viscera, there is an outward flow of fluid and this Horsley takes to be the expression of reversal of the circulation. In the pleura or peritoneum the lymph flow is reversed and the lymph is emptied out around the foreign material. A splinter in the finger becomes surrounded by secretions because the lymph flow has been reversed and eventually is freed from the tissues in which it lies and sometimes is evacuated spontaneously. In all such cases in which there is a secretion or excretion produced by a foreign material Horsley believes it is the reversal of the circulation of the lymph or the blood that is the essential condition for healing, or, at least, for the attempt at evacuating the offending noxa. In his own words, "the reversal of the circulation is the chief biologic process by which surgical drainage acts beneficially in solid soft tissue," etc. Surgical drainage

[1]Horsley: Journal Am. Med. Assn., 1920, lxxiv, 159.

is merely the surgeon's effort to assist Nature,—which is a good point of view, and one often lost sight of.

But we may question whether this conception (of reversal of the circulation) is based upon facts. Is there such a thing as reversal of the lymph circulation or of the blood circulation? We believe not. Even if there be such a physiologic possibility, as for instance in the pleura, would that necessarily account for the pouring out of lymph? It seems impossible. The lymphatics are not provided with openings. The same is true of the capillaries of the blood circulation. As a matter of fact the entire circulatory system is a completely closed one. The reason why lymph is poured out into cavities or into solid tissues is because the chemical conditions outside the vessels are such that more water is needed there because of chemical changes that have changed the physical and chemical characters of the tissue cells. A need for water always exists outside the vessels and so water is always passing outward. Under abnormal conditions the need is accentuated and therefore is the water-transport. An infection, a trauma, (an infection is a chemical trauma as a rule) changes the metabolism and hastens its rate, in the affected tissues; the intermediate and end-products are formed more rapidly, and these are less rapidly carried away. The walls of the capillaries become more permeable, and instead of mere water transport, there is transport of other materials, such as proteins and cells which filter out, so to speak, through the edematous though continuous vessel walls. Depending upon the degree of the changes in the vascular tissue, serum albumin passes out with the water, if the damage is slight, and we have a serous exudate; or, if the damage is greater, serum albumin and fibrinogen pass out together and we get a plastic exudate. In other words a soluble protein like fibrinogen passes through the vessel walls less easily than does another soluble one. This is evidence of the physicochemical nature of the process and evidence against its purely mechanical nature. Beside, if one needs to flush the body as a whole, which is done with diuretics and cathartics, producing what may be called general drainage, one isn't reversing the whole circulation.

Surgical drainage is a mere mechanical addition to the natural process and being that, one would expect that it would usually be combined with methods which accentuate the normal physical process. From any area of infection, whether it be drained mechanically or not, there is some absorption. Soluble toxins and toxic substances pass into the body, and whatever may be said of the bacteria themselves, these toxic substances can be diluted and washed out—drained out—of the body. We speak of surgical drainage, which is physical. Why not also speak of medical drainage which is fundamentally chemical? Diuretics and cathartics act chemically for the most part, at least that is true of the salines. Both exert enormous flushing action on the body, provided enough water is given with them. In cases of infection in which it is desired to dilute the toxins and wash the tissues a certain result is obtained with a concentrated saline which draws water from the tissues. Thereupon the tissues need more water in order to preserve their normal concentration. Surgical drainage takes care of gross exudates; medical takes care of smaller ones and of the soluble materials absorbed into the body. So, it seems, that to obtain the best results, a combination of the two methods is logical. —*P. G. W.*

The Treatment of Gonorrhea

DURING the war specialists had abundant opportunity to test the efficiency of various forms of treatment in gonorrhea. In every camp there were hundreds of cases. We shall pass over attempts to treat this disease by vaccines and serums and confine ourselves to antiseptic injections. In some of the camps there was considerable enthusiasm about the results obtained with certain diffusible dyes. When dissolved in water it was found that many of these preparations were highly germicidal, but, unfortunately, when dissolved in urine the germicidal coefficient fell in most instances to a low point. Among all the diffusible dyes tried there were four found to have a high germicidal action in urine as well as in water. These are: malachite green, brilliant green, proflavine, and acriflavine. There was considerable enthusiasm about the last mentioned preparation and it was believed, for a while at least, that the acme had been reached in the search for a chemical agent which would destroy the gonococcus in dilute solutions and would do no harm to the tissue. Experiments showed that acriflavine inhibits the growth of the gonococcus in a dilution of 1-300,000. This is about 600 times the strength of protargol.

More recently, Young, White, and Swartz[1] have reported a preparation which, in their opinion, is far superior to acriflavine. This substance they name mercurochrome, which is a dibrom-fluorescein into the molecule of which an atom of mercury has been introduced. The sodium salt of this compound is the preparation employed and it contains 26 per cent of mercury. According to the authors, the free acid is a red powder, insoluble in water but readily soluble in alkali, forming a fluorescent solution. The salt appears in iridescent green scales. It is slightly hygroscopic and is readily soluble in water. The solution is stable and bears without change exposure to air and moderate heat. Strongly acid urine gives a slight precipitate of the free dye, but in ordinary urine no such change occurs. The solution stains the skin a bright red color, but this is easily removed by washing first with a 2 per cent solution of potassium permanganate and then with a 2 per cent solution of oxalic acid.

In order to determine the penetration of the mucous membrane by this substance, a solution was injected into the bladder of a rabbit. The drug was allowed to remain in the cavity for five minutes, after which it was drawn out and the rabbit quickly killed. Sections made immediately after death showed that the dye had stained the cells of the superficial epithelium and in some places had penetrated even to the muscular coat. Injection of the solution into the ureter showed that the pelvis of the kidney and the renal tubules were stained for a distance from the vertices of the pyramids. Its toxicity was found by experiment upon rabbits and dogs. Intravenous injections of ten milligrams per kilogram, body weight, killed rabbits, but dogs easily tolerated this amount. This seems to justify the authors in claiming that, as used in the treatment of gonorrhea, there is no probability of poisoning the patient. When injected into the genitourinary tract of man there is said to be no sign of irritation. However, if there be a chronic cystitis there may be some complaint of a burning sensation. The authors evidently have gone quite fully into the germicidal action of

[1]Young, White and Swartz: Jour. Am. Med. Assn., lxxiii, 1483.

this agent. They give tables showing the results obtained and make the following statement: "Acriflavine is shown to be much less potent as a germicide in even the most concentrated solutions, if allowed to act on the organisms for one hour or less. It surpasses mercurochrome in the twenty-four hour test, at this time period, appearing to be about four times as effective as the mercury compound. It is hardly logical to judge a local urinary germicide by its action on organisms during such a long period of time; a short period of exposure in the test, on the other hand, approximates clinical conditions. If rapid disinfection is a desideratum, as it seems to be, mercurochrome is superior to acriflavine."

They also state: "The outstanding fact observed on comparing the germicidal values of mercurochrome, acriflavine, protargol, and argyrol, is the rapidity of action of the mercury compound in fairly high dilutions. In one minute it kills B. coli or Staph. aureus in a dilution of about 1:1,000, a result obtained with none of the other drugs even in one hour. In fifteen minutes its effect is nearly as great as in twenty-four hours, killing B. coli in this short time at 1:5,000 and S. aureus at 1:10,000. A few tests were made to learn the minimal time in which a 1:100 solution would sterilize. S. aureus was killed almost instantaneously; that is, as rapidly as we could introduce the drug, withdraw a sample, dilute in water (to dilute the drug out of action in the agar) and plate. This procedure took no longer than ten seconds. The same test on B. coli revealed that a few organisms remained after ten seconds exposure to the drug. Since a 1:800 solution kills this organism in one minute, the time necessary for a 1:100 solution to kill is possibly not more than thirty seconds."

We earnestly hope that these investigators have not been over sanguine in their claims for the new remedy. We have no doubt that it will be tried by many experts along this line and comparisons will be made not only with other dyes, but with the old silver compounds and potassium permanganate solutions. There is an old saying that there is nothing that lies like figures. Every man who has done experimental work no doubt is ready to say that nothing lies like the first experiments a man makes. He is seldom able to confirm them in full.

—V. C. V.

The Tuberculosis Problem in England

UNDOUBTEDLY the war has greatly strengthened the tendency to the centralization of authority. This applies not only to military matters, but to economic, social, and public health conditions. In England, a Ministry of Health has been established. The British Journal of Tuberculosis for July, 1919, contains a very interesting symposium on the relation of the Ministry of Health to the tuberculosis problem. We propose to briefly review some of the statements made in this symposium.

Woodhead and Varrier-Jones, the former professor of Pathology in the University of Cambridge and the latter superintendent of one of the best known tuberculosis colonies in England, state that the conditions favorable to the spread of tuberculosis have greatly increased during the war. Soon after war was de-

clared there was a rapid rise in the tuberculosis case-rate not only among soldiers, but among the civil population. This increase in morbidity from this disease has continued throughout the war period and probably will continue for some time to come. The new Ministry of Health, no doubt, will be able to deal with a number of health problems that have long called for attention, but undoubtedly it will have its difficulties. Much good work has already been done through dispensaries, sanatoria, and colonies. The writers believe that the Ministry of Health will do well to assist the agencies already in operation rather than to take over under its control all this work.

Oliver states that the time has not yet come for the establishment of a tuberculosis department in the state. For the present the prevention and care of this disease should continue to be a part of the public health service. Hitherto the treatment of the disease has received the greater part of our energy. The results of treatment have not been satisfactory. It is true that life has been lengthened, but this has only given further opportunities for the spread of infection. In the future prevention will occupy a more important place. Control of the milk supply is necessary. In Birmingham the mortality rate has fallen during the last sixteen years from 0.52 per 1,000 to 0.26. This decline to one-half the death-rate from all causes does not apply to pulmonary tuberculosis. During the war the incidence and mortality rate of this disease increased. As housing, feeding, and occupation are three of the circumstances of our social life under which tuberculosis will have to be tackled, there must be harmony of action between the Ministry of Health, Municipalities, and Medical Officers of Health.

Lumsden admits that the war against tuberculosis in Great Britain and Ireland has been largely a failure and that much public money has been spent without corresponding results. He believes that the problem of the advanced consumptive is of the most importance. All cases of open tuberculosis should be segregated and so placed that the spread of the disease is impossible. He says: "We have been traveling in a circle—first we send unsuitable cases to sanatoria, informing the patient we hope to cure him, and we then permit him to return to his old environment without effort to improve it or to properly supervise his home and its unhealthy devitalizing condition. Recrudescence or reinfection commonly occurs, the patient once more becomes a focus of infection for his family and the community, and he returns from the sanatorium for the tragedy to be played out to its disastrous end. Until this vicious circle is broken tuberculosis will surely remain with us, and public money will be spent without any finality being attained. The tragic feature of this urgent and colossal problem is that we now know how the disease can be stamped out, but for sentimental reasons we lack the pluck to tackle it by putting into force the necessary machinery. In my humble judgment a thoroughly efficient and strong tuberculosis department, with all the necessary powers, should be instituted under the new Ministry of Health. Housing, provision of a clean milk supply, tuberculosis and other dispensaries, school inspection, etc., are all essential factors no doubt, but one of the first efforts should be to secure the segregation or control of all tuberculous cases of an infectious nature. The disease should be made compulsorily notifiable, the home should be inspected by the local authority,

and one of the two following courses adopted: (1) Proper sleeping and living conditions established so that infection shall be reduced to a minimum, which we know can be done in most cases with small expense, and generally with the family's cooperation, once the position is made clear to them; (2) If this course can not be accomplished the patient should be compulsorily removed to a home where he can no longer spread his infection."

Hope, a health officer of Liverpool, believes that the Ministry of Health, acting as a central and authoritative body, will link up and make more effective the local agencies. He says: "In dealing with housing, maternity, and infant welfare, pure milk supply, open-air schools, hospitals for advanced cases, industrial colonies, discharged soldiers, etc., the multiplicity of authorities to be considered and consulted has led almost inevitably to some amount of friction and overlapping, with all the resulting waste of effort, time, money, and lives, that such friction and overlapping involve. It is to the new Ministry of Health—which should be able to unify, to direct, to control, and, it may be presumed, will be provided with the necessary powers and money to insure its orders being carried out—that we must look in future for the solution of a problem that is even more urgent now than it was in pre-war days."

Hill, of the London Hospital Medical School, seems inclined to the opinion that insanitary housing is the most important factor in maintaining the high prevalence of tuberculosis. He states that the expectation of life at birth is sixteen years less in insanitary districts than it is in the healthiest communities, while the mortality of children under five years is more than twice as great. He believes that the Ministry of Health must concentrate on the rebuilding of the industrial centers of England, as garden cities, where open-air exercise can balance sedentary indoor work, and fresh, green foods be grown in the gardens and abundantly supplied to the people. At the same time, the children must be educated in the discipline of maintaining their health. He adds that the present conditions of housing and factory life make more sick and inefficient people and kill more than the late war year by year.

O'Donovan, of the Ministry of Munitions, thinks that special attention must be given to the prevention or arrest of tuberculosis among industrial workers. One important thing is the detection of early cases and the prompt attention to such cases. In the interest of the workers and of the community a factory medical service seems to be the only way in which the early detection of phthisis will be practicable in an industrial community. Repeated absences from work should lead to inquiry. The absentees should be sought and it should be ascertained whether their absence is due to failure in health.

Vining, of Leeds, calls attention to the great importance of milk in the spread of tuberculosis in infancy. He thinks that the Ministry can proceed to provide ways and means for the sterilization of milk throughout the country and should insist that every infant be fed upon sterilized milk.

Buckley, director of milk supplies, Ministry of Food, quite naturally emphasizes the importance of milk. He says that about forty per cent of the cattle in England react to the tuberculin test; also that ten per cent of the milk that reaches the large towns contains tubercle bacilli. He says, however, that this does not mean that ten per cent of the cows yield tubercular milk, but since the

milk from different animals is mixed he thinks it a fair estimate to say that one per cent of the animals are infected. He calls attention to the fact that manure in stables, even where only a small per cent of the herd may be infected, may contain tubercle bacilli and these find their way into the milk. He says there are two ways of insuring that milk as it reaches the consumer shall not contain living tubercle bacilli. The first is to test every milch-cow with tuberculin and to exclude from the herd all those giving positive reactions. The second method is to properly pasteurize all milk.

Bullock, of St. Leonards-on-Sea, says that the Ministry of Health should insure that a certain proportion of new houses to be built have an open and sunny aspect, and so long as home treatment is applied to the advanced consumptive, at least one sunny room on the ground floor should be available for the patient. He thinks that the inspection of factories should be more stringent and that the provisions against overcrowding, imperfect ventilation, etc., should be more earnestly enforced. In addition to the possibility of infection through milk in childhood, he insists that many poor children do not have enough milk to drink. Of course, the milk should be free from infection, and at the same time there should be enough of it to furnish the child with the proper quantity of food.

Wingfield, of St. Thomas Hospital, advocates placing all matters pertaining to tuberculosis in the hands of the Ministry of Health. At present, tuberculosis sanatoria, hospitals, colonies, etc., are supported and controlled by local authorities. He thinks that all this must pass away. The Ministry of Health must be a strong central body. It should divide the whole Kingdom into areas, each of which must not supply more than 2,000 patients per year. For these units there must be tuberculosis officers, responsible only to the Ministry of Health. This tuberculosis officer must be capable of dealing with all forms of the disease and should have had, previous to assuming his duties, a thorough course of training at some recognized center of tuberculosis work. On him must rest all the responsibility for the work of the district. He should have a definite number of beds for advanced cases, for latent cases, for those who can do some work, etc. No cases should be treated at home. The number of beds should be at least fourteen per cent of all reported cases in the community. The hospital and the sanatorium should be in the same institution. There should be a hospital sorting house in every large town. There should be local homes for advanced cases and these should be attached to each unit. Beds for this purpose will reach two per cent of all patients treated. The patient who has improved in the sanatorium must be taken care of later by the state. This should not be regarded as a charity but as a duty. The Ministry of Health must concentrate on the after-care of patients before all else. If proper after-care was insisted upon now and proper facilities provided for it, the usefulness of our present tuberculosis scheme would increase by ten per cent. The present system of after-care is cumbersome and in actual practice has proved useless.

—*V. C. V.*

Tuberculosis in the French Army During the War

IT will be remembered that in 1917 this country was greatly alarmed by the statement that tuberculosis was vying with the Hun in its deadly warfare on the French soldier. It seems that this alarm came in the first place from French sources. Professor Landouzy, who has visited this country and is more or less well known and appreciated here, estimated the discharges from the French Army from tuberculosis in 1917 at 150,000. In December, 1917, M. Godart stated in the French Senate that the total number of soldiers discharged from the French Army from August 2, 1914, to October 31, 1917, was 89,430. Of these, 70,196 had been discharged prior to March 1, 1916, and they were cases of pre-existing tuberculosis which were accepted for service in 1914 when overthrow of the country was threatened. Later it was shown, especially by Major Rist, that at least forty per cent of these cases had been incorrectly diagnosed and were not tuberculosis after all.

Miller[1] says: "The exact size of the French Army is not public knowledge so that accurate estimate of the meaning of these figures in percentages is not possible, but it certainly could not have been less than 4,000,000 men the first months of the war or less than 3,000,000 in the latter period after March 1, 1916. Upon this basis and accepting the higher figures furnished by M. Godart as official, without consideration of the tremendous reduction which would result from the acceptance of the estimates of Messrs. Sergent and Rist, we may estimate that the maximum amount of tuberculosis necessitating discharge from the army was 1.75 per cent in the early months of the war, when according to general knowledge large numbers of active cases of tuberculosis were mobilized, and 0.63 per cent in the later months of the war after such cases were probably largely eliminated."

According to Bushnell, an average of 0.78 per cent was rejected for tuberculosis in this country. Miller thinks that this indicates, not only that the tuberculosis situation in the French Army was exaggerated, but also that the number of cases developing in the army during active service is not greater than that found in a similar group of men taken from civilian life in America.

—*V. C. V.*

Typhoid Fever in Flanders

GOODALL[1] has given a most interesting account of typhoid fever in Flanders during the fall, winter, and spring of 1914-1915. It seems that this disease was widely prevalent, though not alarmingly so, in Belgium at the time of the German invasion in August, 1914. The people from eastern Belgium fled westward, without adequate supplies of any kind, and even without the necessities of life. Western Belgium is a plain, intersected by rivers, canals and ditches, in all of which the water flows very slowly. This plain is highly cultivated and is manured largely with human excreta. The water-supply in the villages is

[1]Miller, James A.: Am. Rev. Tuber., iii, 339.
[1]Goodall, E. W.: Proc. Roy. Soc. Med., xii, 15.

drawn largely from shallow wells. Wherever this condition exists typhoid fever is endemic. In the fall of 1914, there were four armies in this region—the British, French, and Belgian on one side and the German on the other. The only one of these armies at that time vaccinated was the British, and these soldiers had been vaccinated against only the Eberthian bacillus, while the typhoid fever prevalent at the time was paratyphoid. According to Goodall, there were many thousand cases of typhoid fever among the civilians in the region about Ypres in the fall of 1914. We have no definite information concerning the number of cases in the German Army, but we have intimation that it was quite large. The English took hold of the sanitation of the district positively and most effectively. Orders were issued compelling not only soldiers, but all civilians to be vaccinated. The drinking water was sterilized with chlorin and was dealt out to the population, both military and civil. The value of chlorination of water was apparently demonstrated. At Ypres the water-supply before the war was good. The water tower was not destroyed until the summer of 1915, but in September, 1914, this water-supply was not available because the mains had been broken. The English cleaned a large swimming tank in Ypres, lifted water knowingly polluted from the canals, treated it with chlorin and stored it in the swimming tank, from which it was dealt out to the population. The interesting part of it is that the English cleaned up the region so thoroughly that by the spring of 1915, the epidemic had ceased entirely and there was no return of it at any time during the war. Usually Eberthian typhoid is much more fatal than the paratyphoids, but this was not always the case in the local epidemics that occurred in Flanders. In one hospital the mortality from typhoid fever was 9.7 per cent, while that from paratyphoid in the same hospital was 19.2. Goodall is inclined to attribute the great success that the English had in cleaning up on typhoid fever around Ypres to the sanitary methods rather than to vaccination, because he says that up to that time they vaccinated against only Eberthian typhoid and the typhoid prevalent there was paratyphoid.

It may be interesting to note in this connection that in November, 1914, an epidemic of typhoid fever appeared in the French Army in the region of Belfort. It spread rapidly from the Swiss border to the sea and became alarming in December, 1914, and January, 1915, when it reached a maximum of 7.24 per 1,000. Systematic and thorough vaccination was begun during this period. Typhoid fever rapidly disappeared. Vincent states that had the typhoid rate of December, 1914, and January, 1915, continued during the thirty-eight months of actual hostilities, there would have been in the whole French Army of between four and five million men not less than 1,000,000 cases and 145,000 deaths. He states further that compared with the morbidity and mortality rates in the whole French population before the war, the morbidity from this disease in the French Army during the war was one-seventh and the deaths about one-eighth of what they were in peace times. From August 3, 1914, to September 1, 1917, the French Army Medical Laboratory sent to the front 5,513,073 doses of vaccine. —*V. C. V.*

Staining Tubercle Bacilli

GOECKEL[1] has developed a convenient method for concentrating and isolating the tubercle bacilli. It is usual now to treat tuberculous sputum with antiformin, which is a strong solution of sodium hydroxide and sodium hypochlorite. This preparation dissolves the other constituents of the sputum but leaves the tubercle bacilli untouched. Goeckel proposes to substitute for antiformin Rice's Bromine and Alkali Reagent, which is used for determining urea in the urine. Rice's Solution No. 1 consists of:

Bromine	30 gm.
Sodium Bromide	30 gm.
Distilled water	250 c.c.

Solution No. 2 is as follows:

Sodium hydroxide	70 gm.
Distilled water	250 c.c.

The technic of Goeckel is the following: To the sputum or other tissue to be examined add a few c.c. of Rice's Solution No. 2, mix well, and add Rice's Solution No. 1 in successive small portions until a clear fluid is obtained. The use of heat is not necessary. The liquid is diluted with distilled water and is centrifuged at high speed to precipitate the bacilli. These are then washed with two successive portions of distilled water, centrifuging to remove the alkali. The residue is placed on a microscopic slide, fixed with a trace of albumin, and stained.

—*V. C. V.*

The Treatment of Tuberculosis Cervical Adenitis

ABBOTT[1] holds that in the treatment of this condition we should first attempt to prevent further infection. This can be accomplished, in part at least, by attention to the mouth and throat. Any decayed teeth should be attended to by the dentist. The tooth brush and other methods of cleaning the oral cavity should be resorted to. Hypertrophied tonsils and adenoids should be removed, and any discharges from the nose or ear should be properly treated. The patient, although it is too late to prevent primary infection, should sleep out-of-doors, and have an abundance of properly balanced food. The time-honored syrup of iodide of iron should be tried. In some instances potassium iodide may be of benefit, and according to the author never induces any untoward effect.

Abbott gives first place in the treatment of these glands to tuberculin. He says that he has frequently been consulted by patients seeking to avoid operation, who have patiently plodded the long road of palliative treatment, who have become discouraged and were about to turn to the scalpel as their only hope—he has seen these restored to a perfectly normal condition by the intelligent use of tuberculin. He thinks that tuberculin acts by increasing the formation of

[1]Goeckel, Henry J.: Med. Rec., New York, November 15, 1919.
[1]Abbott, Wilson Ruffin: Am. Rev. Tuber., iii, 175.

fibrous tissue and that this hyperplasia is associated with the protective deposits of mineral salts. In this way progression towards suppuration is arrested and eventually contraction of the fibrous tissues causes a general regression in the size of the glands.

When other measures fail surgical operation should be resorted to. Abbott adds that one should not wait until the glands have broken down, ruptured their capsules and matted together, because by that time the deeper lymphatics will have become involved and the boundaries of the triangle will have been passed. To the reviewer's mind, it seems that trusting to medicinal treatment, whether it be iodide or tuberculin, is in fact delaying too long and that surgical operation should be performed immediately when involvement is confined to the superficial glands.

Abbott is quite sure that, in many instances at least, a cure can be secured by the surgical removal of the infected glands but that this is possible only when the invasion is limited to the triangular area. Moreover, the removal of the infected glands, if done soon enough, will prevent penetration to the deeper lymphatics and possibly the later development of pulmonary tuberculosis. The best results are obtained in children under ten years of age. —*V. C. V.*